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Glycosylated vinyl ethers by the Julia–Lythgoe–Kocienski olefination: application to the synthesis of 2′,5′-dideoxydisaccharides and carbohydrated β-lactams

Iván Pérez Sánchez, Edward Turos *

Center for Molecular Diversity in Drug Design, Discovery, and Delivery, Department of Chemistry, University of South Florida CHE 205, 4202 East Fowler Avenue, Tampa, FL 33620, USA

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ABSTRACT

α-Carbohydrated pyridinyl sulfones, prepared from commercially available D-(−)-ribose, D-(+)-galactose, and D-(+)-glucose through a five-step sequence, have been employed in the Julia–Lythgoe–Kocienski olefination with aldehydes. This one-pot protocol, using solid KOH at room temperature, affords the corresponding glycosidic enol ethers in moderate to excellent yields and (*E*)-stereoselectivities. These glycosylated adducts undergo hetero-Diels–Alder reactions with 2-formyl-1-malondialdehyde to afford 2′,5′-dideoxygenated disaccharides in good yields and complete regio- and *endo*-selectivity. Alternatively, the [2+2]-cycloaddition reaction of the glycosidic enol ethers with chlorosulfonyl isocyanate provided glycosylated β-lactams regioselectively and with only *trans*-stereoselectivity. The β-lactams could be converted to *N*-methylthio derivatives which show decent antibacterial activity toward methicillin-resistant strains of *Staphylococcus aureus*.

1. Introduction

The construction of functionalized carbon–carbon double bonds has remained among the most investigated and important synthetic transformations, spawning the development of various new methodologies which enable the efficient construction of highly substituted olefins with control of double bond geometry.[1] One of the most employed examples among these is the classical Julia coupling, also known as the Julia–Lythgoe olefination.[2] Disclosed more than 30 years ago, the Julia coupling employs a reductive elimination of β-acyloxy phenyl sulfones, which can be prepared by the addition of phenylsulfonyl-stabilized carbanions to carbonyl compounds, with conversion of the resulting alcohol to the acyl ester. Since its discovery, significant advances have been made to further improve the efficiency of the reaction, as well as to apply its use as a key step in natural products synthesis.[3] A recent variant of this reaction, the Julia–Lythgoe–Kocienski olefination, offers a convenient one-pot coupling procedure that has emerged as a powerful synthetic tool. Its novelty stems from the replacement of the commonly used phenylsulfonyl stabilizing moiety for a *heteroarylsulfonyl* group, which permits the spontaneous elimination of the sulfonic acid and concomitant formation of the desired olefin in a single operation.[4]

In our studies relating to the development of methods for glycosylation, we aimed to apply this popular and powerful methodology to yet another historically important area of synthesis, carbohydrates, through the development of glycosylated Julia reagents.[5] As we began this study, we succeeded in finding only one prior publication of an α-alkoxysulfone being employed in a Julia olefination.[6]

Herein we report the preparation of the requisite α-carbohydrated pyridinylsulfones and some representative examples of their reactions with aldehydes to prepare carbohydrated enol ethers. We then explore the application of these adducts to the synthesis of disaccharides and carbohydrated β-lactams by cycloaddition with 2-formyl-1-malondialdehyde and chlorosulfonyl isocyanate, respectively.

2. Results and discussion

2.1. Preparation of α-glycosyloxymethyl pyridin-2-ylsulfones 5

For this study, we focused on several pyridin-2-ylsulfones **5**. These were readily prepared by reaction of 2-mercaptopyridine with the corresponding *O*-chloromethyl glycoside **3** using NaH as base and NaI as an anion transfer agent in THF at room temperature, to give sulfides **4** (Scheme 1). Subsequently, oxidation with *m*-CPBA in the presence of a buffer solution of Na_2HPO_4 or with hydrogen peroxide (30% H_2O_2) and a catalytic amount of sodium tungstate ($Na_2WO_4{\cdot}2H_2O$) 10 mol % in methanol gave sulfones **5**. The requisite chloromethyl glycosides **3a–d** for these syntheses were prepared from the corresponding acetonide-protected monosaccharides **1a–d** using sodium hydride as a base and

* Corresponding author. Tel.: +1 813 974 7312; fax: +1 813 974 1733.
E-mail address: eturos@cas.esf.edu (E. Turos).

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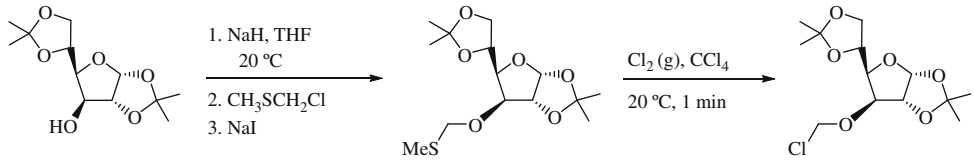
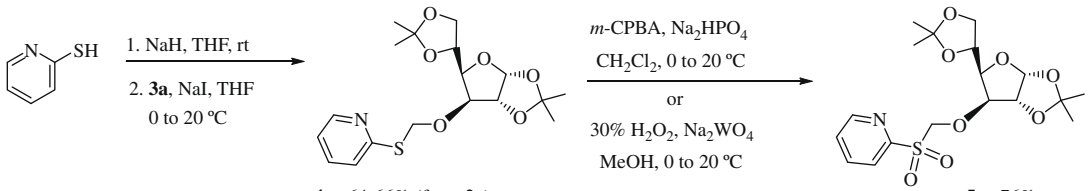
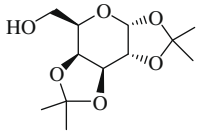
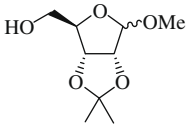
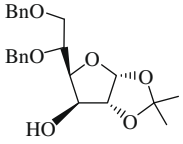


1a **2a** 71-89% **3a** >95%



4a 64-66% (from **2a**) **5a** 76%

1		2	Yield %	3	Yield %	4	Yield %	5	Yield %
1b			77	**3b**	>95	**4b**	73	**5b**	77
1c		**2c**	72	**3c**	>95	**4c**	86	**5c**	78
1d			See compounds **6** and **7** in Scheme 2	**3d**	>95	**4d**	86	**5d**	86

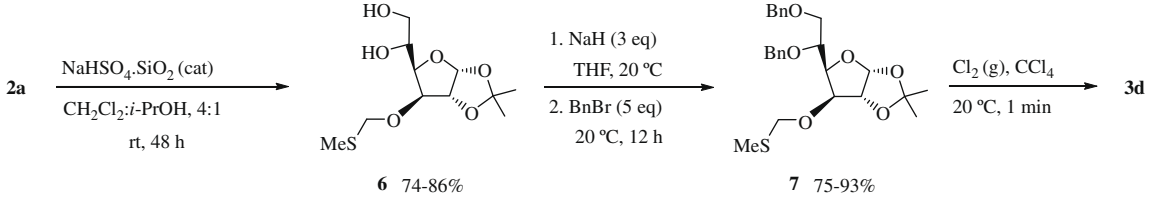
Scheme 1. Synthesis of glycosylated pyridin-2-ylsulfones **5a–d**.

methylthiomethylene chloride followed by the addition of NaI to give the O-alkylated product **2**, which was then converted by chlorination to chloromethyl derivatives **3**. Overall isolated yields for this two-step transformation ranged from 60% to 85%. In the case of preparing compound **3d**, the extra-annular acetonide moiety of **2a** was first replaced with benzyl groups to give sulfide **7** prior to sulfone formation (Scheme 2).

2.2. Julia–Lythgoe–Kocienski synthesis of ethenyl ethers 8

We initiated our studies of the olefination reactions using these glycosylated sulfone reagents by examining different bases such as KHMDS, LiHMDS, BuLi, and KOH, either at room temperature (KOH) or at low temperatures (−78 °C for KHMDS, LiHMDS, and BuLi and −25 °C for KHMDS) in THF, DME, or toluene as solvents. The best results were observed using solid KOH pellets in anhydrous THF in the presence of tetrabutylammonium bromide (TBAB). Using these conditions, we examined the olefination reactions of sulfones **5a–d** with a representative variety of non-enolizable aldehydes to further evaluate the scope and limitations (Table 1).

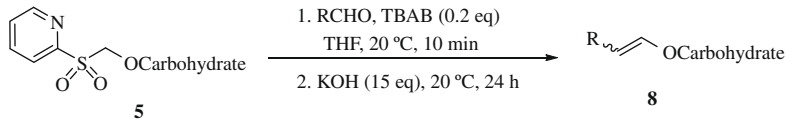
In terms of scope, this single-pot coupling reaction proceeded successfully and with good to excellent efficiency with benzaldehyde to afford ethenyl ethers **8a**,**c**,**g**,**o** in 63–78% yields (entries 1, 3, 7, and 15). The same was the case for aryl aldehydes bearing electron-donating substituents to give ethenyl ethers **8d**,**e**,**h**,**i**,**l**,**m** in 70–91% yields (entries 4, 5, 8, 9, 12, and 13), and with 2-furaldehyde, which afforded **8n** in 92% yield (entry 14). However, the



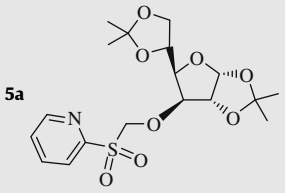
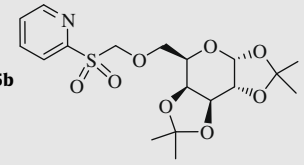
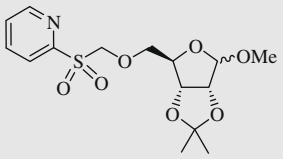
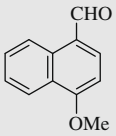
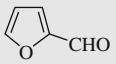
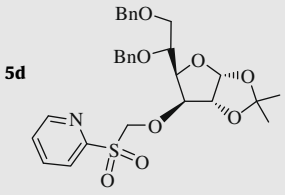
6 74-86% **7** 75-93%

Scheme 2. Synthesis of *O*-chloromethyl glycoside **3d**.

Table 1
Glycosylated enol ethers **8a–r** produced via the Julia–Kocienski olefination



5 **8**

Entry	Sulfone **5**	RCHO	Enol ether **8**	Yield[a] (%)	*E*/*Z*[b]
1	 **5a**	PhCHO	**8a**	63	75/25
2		4-FC_6H_4CHO	**8b**	54	75/25
3	 **5b**	PhCHO	**8c**	71	96/4[c]
4		4-$MeOC_6H_4CHO$	**8d**	91	89/11
5		2-$MeOC_6H_4CHO$	**8e**	78	89/11
6		4-FC_6H_4CHO	**8f**	40	93/7
7		PhCHO	**8g**	72	94/6[c]
8		4-$MeOC_6H_4CHO$	**8h**	88	78/22
9		2-$MeOC_6H_4CHO$	**8i**	83	71/29
10		4-ClC_6H_4CHO	**8j**	48	92/8
11		2-ClC_6H_4CHO	**8k**	45	78/22
12	 **5c**		**8l**	70	81/19
13		4-$Me_2NC_6H_4CHO$	**8m**	81	86/14
14			**8n**	92	67/33[d]
15	 **5d**	PhCHO	**8o**	78	71/29
16		*t*-BuCHO	**8p**	31	>1/99
17		4-FC_6H_4CHO	**8q**	58	69/31

[a] Isolated yield after flash chromatography.
[b] Determined by ^1H NMR of the crude reaction mixture. Most enol ether mixtures can be enriched in one or the other diastereoisomer after column chromatography.
[c] The major diastereomer (*E*) was isolated by column chromatography.
[d] Diastereomers were separated by column chromatography.

yield of the coupling reaction dropped drastically (31–58%) when electron-deficient haloaryl aldehydes (entries 2, 6, 10, 11, and 17) or the bulky trimethylacetaldehyde (entry 16) was used as substrate. The (*E*)-stereoselectivity was high with neutral or electron-poor aromatic aldehydes, and decreased slightly when electron-rich aromatic aldehydes or heteroaryl aldehydes were employed. It is noteworthy that the olefination reaction with pivaldehyde afforded the corresponding enol ether **8p** with an opposite (reversed) sense of stereoselectivity (geometry) [only the (*Z*)-isomer], which was evident from its ^1H NMR spectrum. This indicates that *E*-stereoselection may be partially governed by the steric demands of the aldehyde. With respect to sulfone **5**, we observed no discernible differences in the yield of the reaction when galactose **5b**, ribose **5c**, or glucoses **5a,d** sulfone derivatives were used with benzaldehyde in the presence of KOH and TBAB: galactosyl and ribosyl sulfones, **5b** and **5c**, afforded ethenyl ethers **8c** and **8g** in 71% and 72% yield, respectively, and with excellent diastereoselectivities (*E*/*Z* 96:4 and 94:6) (Table 1, entries 3 and 7). The analogous use of the two glucosyl sulfones **5a** and **5d** led to enol ethers **8a** and **8o** (63% and 78%, respectively) but with a markedly lower *E*-selectivity (*E*/*Z* 75:25 and 71:29) (Table 1, entries 1 and 15). This indicates that the steric demands of the carbohydrate reagent may affect *E*-stereoselection, with sulfones derived from *secondary* carbohydrate alcohols **5a** and **5d** providing lower *E*-selectivity than those of *primary* alcohols **5b** and **5c**.

In terms of the limitations of the reaction, so far, we have not had success in applying the modified Julia–Lythgoe–Kocienski olefination conditions to the sulfones **5a–d** while attempting to use readily *enolizable* alkyl aldehydes **9–12**, 3-methyl-2-butenal **13**, paraformaldehyde **14**, ethyl glyoxalate **15**, 3-pyridinecarboxaldehyde **16**, 4-nitrobenzaldehyde **17**, methyl 4-formylbenzoate **18**, or 2-(methoxymethyloxy-methyl)benzaldehyde **19** (Fig. 1). In each of these experiments, the corresponding 2-pyridinyl ether derivative **21**, **22**, or **23** was isolated in 30–55% yield. Curiously, these unanticipated products do not retain the initial methylenesulfone unit, which is apparently expelled through a pathway that we have not yet deduced. In analogous reactions, sulfone **5c** and 2-cyanobenzaldehyde **20** afforded approximately 5% of the corresponding enol desired ether **8** based on NMR evaluation of the crude product mixture, which shows signals of clear doublets (J = 12.9 Hz) at δ 5.80 and 7.03 for each of the vinyl protons that correspond to the *E*-isomer of compound **8**. However, this product was not further purified.

The yield and stereoselectivity of these olefinations seem to be sensitive to the nature of the base and solvent used. For instance, reaction of ribosyl pyridinylsulfone **5c** with benzaldehyde, which provided the enol ether **8g** in 72% and 94:6 ratio of *E*/*Z* isomers with solid KOH as a base, gave only a 54% yield and 2.3:1 mixture of *E*/*Z* diastereomers when solid NaOH was used instead. This result shows that both yield and (*E*)-stereoselectivity are diminished when NaOH replaces KOH as base for initiating the coupling. We also attempted, under analogous treatment, the Julia olefination between sulfone **5c** and benzaldehyde using KOH/toluene or LiOH/THF instead of KOH/THF. However, neither gave the ethenyl ether **8g**, presumably due to the poor solubility of the reagents in toluene and the lower basicity of LiOH, respectively. In both instances, the starting materials were recovered upon aqueous workup.

A possible mechanistic explanation for these differences in *E*/*Z* stereoselectivities is depicted in Scheme 3. Initially the sulfonyl carbanion, generated with KOH, reacts with the aldehyde through a non-chelated (or open) transition state **A**, which is favored for polar solvents and large counter cations such as potassium. This kinetically controlled addition preferentially generates the *anti*-β-alkoxysulfone **B**, which decomposes stereospecifically via Smiles rearrangement with spontaneous expulsion of sulfur dioxide and 2-hydroxypyridine to yield the (*E*)-vinyl ether **8**. On the other hand, we suggest that the smaller (harder) sodium cation has a stronger tendency to form a chelated (or closed) transition state **A′** proceeding to the *syn* adduct **B′**, which decomposes stereospecifically to the (*Z*)-vinyl ether **8**. Thus, the use of NaOH in the place of KOH lowers *E*/*Z* stereoselectivity in the olefin formation.

2.3. Reactions with enol ethers 8: hetero-Diels–Alder

Enol ethers have an electron-rich functionality, and are well documented to participate in electrophilic additions or cycloadditions. Simple enol ethers of glycosidic substrates have been prepared by acid-catalyzed elimination of orthoformates and acetals, Tebbe reaction with a glycosidic acetate, base-promoted addition of a glycosidic alcohol to propiolate, and metal-catalyzed *trans*-vinylation of glycosidic acetates.[7–17] The enol ether functionality has been introduced onto the carbohydrate most commonly as a means to facilitate the stereocontrolled introduction of carbon substituents at the anomeric center, and for glycosylation reactions. There are a few other instances involving the use of glycosidic vinyl ethers, such as for polymerization processes or as dienophiles in [2+2] and hetero-Diels–Alder reactions.[16–18] It is the latter applications that we considered of most immediate interest to us, given the propensity and popularity of hetero-Diels–Alder methodology to prepare structurally complex frameworks. In order to establish some preliminary indications on the synthetic utility of these β-substituted enol ether glycosides, we explored their reactivity as dienophiles in hetero-Diels–Alder reactions as illustrated in Scheme 4. In the first example, ethenyl ether **8c** (X = H, 10:1 mixture of *E*/*Z* isomers) in a 10:1 mixture of benzene/CH_2Cl_2 at 82 °C (sealed tube) led, after two days, to the 2′,5′-dideoxydisaccharide aldehyde **25** (X = H) in 77% yield and as an 2:1 mixture of two diastereoisomers (**25a** and **25b**).[19,20] Along with adducts **25**, 15% of starting enol ether **8c** was observed in the crude mixture after workup, as a 1.5:1 mixture of *E*/*Z* isomers. Compounds **25** and **8c** were separated by flash column chromatography. The analogous reaction carried out with alkenyl ethers **8f** (X = F, *E*/*Z* 6.3:1), **8g** (*E*/*Z* 7.5:1), and **8b** (*E*/*Z* 3:1) produced the corresponding annulated adducts **26** (67%), **27** (73%), and **28** (36%), respectively, also as non-separable 2:1, 1.2:1, and 8:1 mixtures of diastereomers, respectively. In each case, we also recovered the corresponding starting enol ethers **8f** (25%, *E*/*Z* 1:1.1), **8g** (20%, *E*/*Z* 1.2:1), and **8b** (57%, *E*/*Z* 2:1) from the reaction mixture after workup. The structure

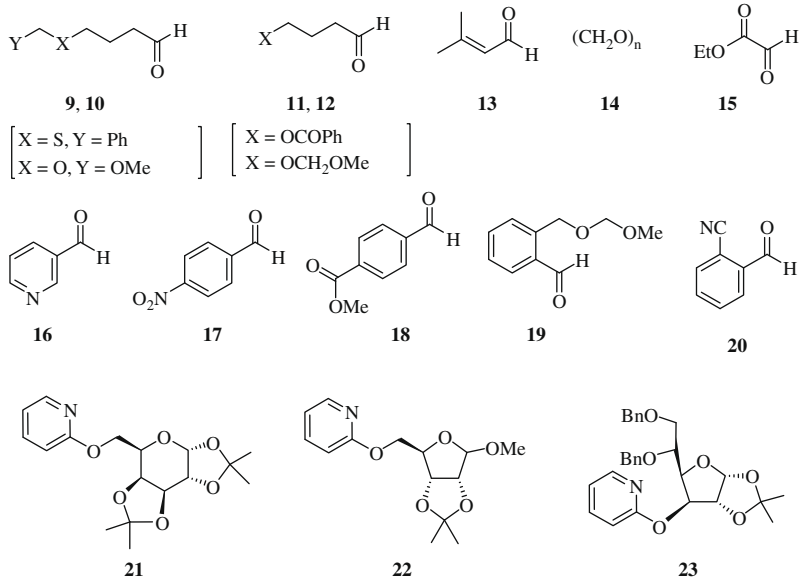
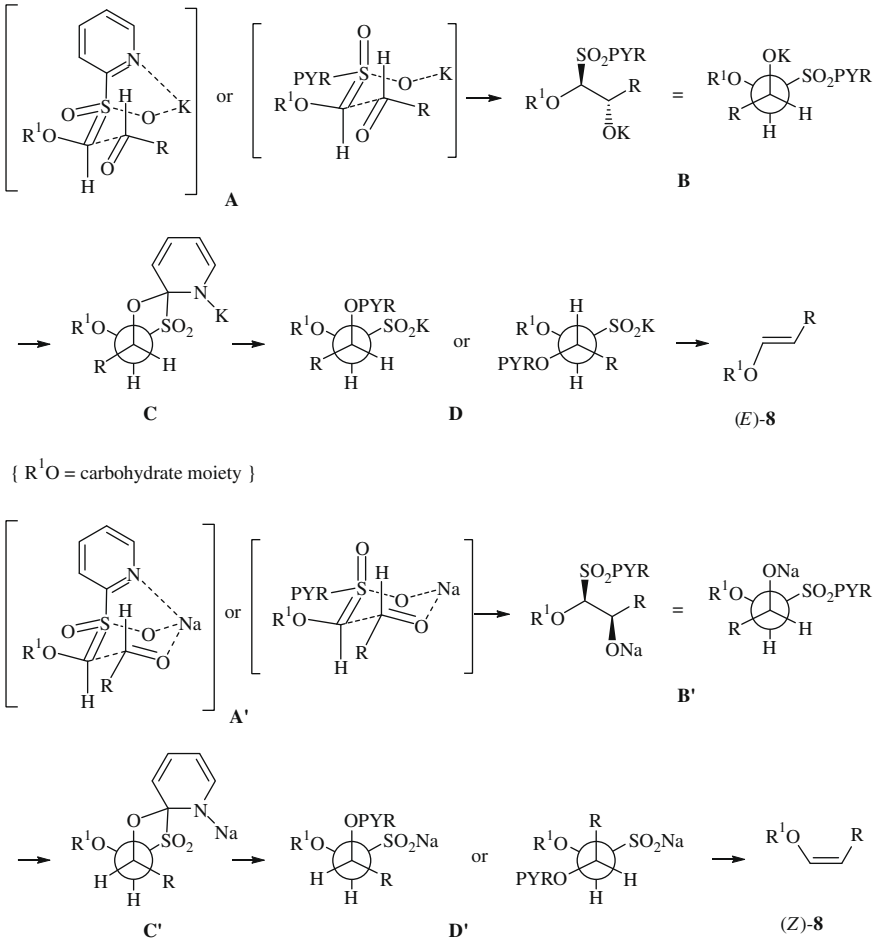


Figure 1. Limitations of the one-pot Julia–Lythgoe–Kocienski olefination with sulfones **5a–d**.



Scheme 3. Proposed mechanism for the origin of *E*/*Z* selectivity.

and relative stereochemistry of the cycloaddition products **25**, **26**, **27**, and **28** were confirmed by 1D and 2D NMR spectroscopic experiments.[21]

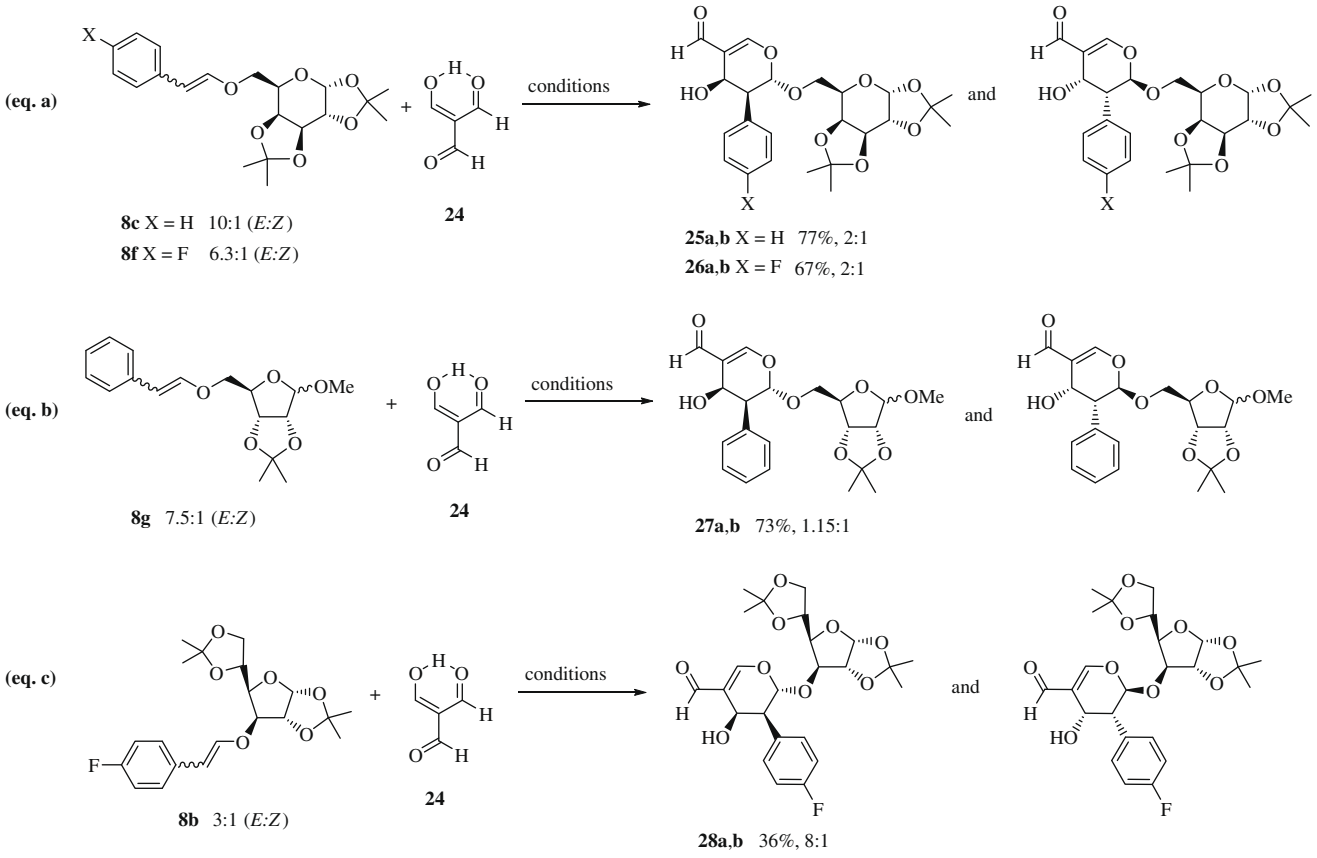
It is interesting that the *E*/*Z* ratios of the recovered starting enol ethers **8** from each of the cycloaddition reactions had an increased amount of *Z*-isomer: **8b,** *E*/*Z* 3:1 (initial) versus 2:1 (recovered); for **8c**, *E*/*Z* 10:1 (initial) versus 1.5:1 (recovered); for **8f**, *E*/*Z* ratio 6.3:1 (initial) versus 1:1 recovered); for **8g,** *E*/*Z* 7.5:1 (initial) versus 1.2:1 (recovered). We attribute this to the strong preference for the *E*-isomer to undergo cycloaddition much more readily than the *Z*-isomer, which remains unreactive in the reaction mixture. This is corroborated with the finding that only the *cis*-disubstituted stereoisomers of cycloadducts **25**, **26**, **27**, and **28** are obtained, all coming from the *E*-enol ether. The [4+2] cycloaddition reactions proceed with complete regio- and *endo*-selectivity and with good yields (67–77%) when primary enol ethers are employed, but the yield drops noticeably when secondary ethenyl ether **8b** (36%) is used. The high *endo* stereocontrol (with respect to the carbohydrate-O moiety) is the result of an expected strong donor–acceptor π-interaction between the oxygen non-bonding electrons of the enol ether and the carbonyl of the aldehyde function (Scheme 5). The corresponding transition states *endo*-***I*** and *endo*-***II*** lead to the two possible *endo* adducts **25a** (or **26a**) and **25b** (or **26b**). Similar transition states would explain the respective formation of the hetero-Diels–Alder products **27a**, **27b**, **28a**, and **28b**. The higher facial diastereoselectivity provided by the enol ethers of secondary alcohol glycosides **8b** versus those of the primary alcohols **8c,f,g** is likely due to greater steric interactions manifested within these π-stacked transition states.

2.4. Reactions with enol ethers 8: [2+2] cycloaddition

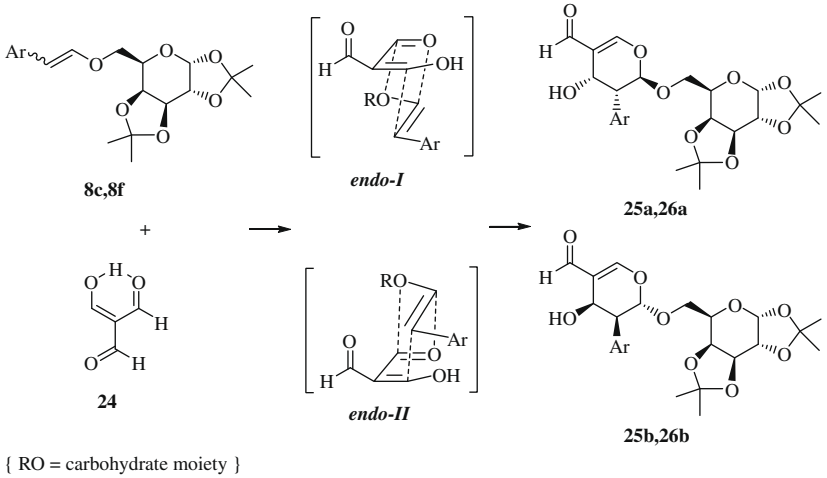
Chlorosulfonyl isocyanate (CSI) is a highly reactive participant in [2+2]-cycloadditions with vinyl ethers, providing an attractive and direct route to substituted β-lactams.[22] Recently, sugar-derived vinyl ethers have been used as chiral starting materials in these cycloadditions for the asymmetric synthesis of β-lactams.[23] Our group has had a longstanding interest in β-lactam chemistry, and in particular, the microbiological activity of N-thiolated β-lactams as mechanistically novel antibiotics.[24] The water solubility of these compounds however is very low, and thus we had hoped to prepare glycosylated β-lactam derivatives for examination. This led us to consider the reaction of the glycosylated enol ethers prepared above for stereocontrolled [2+2]-cycloaddition reactions leading to C_4-glycosylated β-lactams.[22,25]

We first investigated the reaction of chlorosulfonyl isocyanate with galactosyl ethenyl ether **8c** (used as a 40:1 mixture of *E*/*Z* isomers) in toluene in the presence of pulverized anhydrous sodium carbonate (Scheme 6).[26] We noted that the formation of the desired β-lactam and the *N*-chlorosulfonyl group was then removed by Red-Al reduction at 70 °C. After hydrolytic workup, we obtained 3,4-disubstituted β-lactam **29** in 77% yield as a 1.3:1 mixture of diastereomers, which unfortunately could not be separated by flash column chromatography.

The analogous treatment of glycosylated enol ethers **8g** (2.3:1 *E*/*Z*), **8o** (2.3:1 *E*/*Z*), and **8q** (*E*/*Z* 1.2:1) with CSI followed by Red-Al reduction resulted in the formation of the corresponding β-lactams **30**, **31**, and **32**, respectively.[27] While the yields of the latter reactions are similar to that with **8c**, the diastereoselectivity of the cyc-



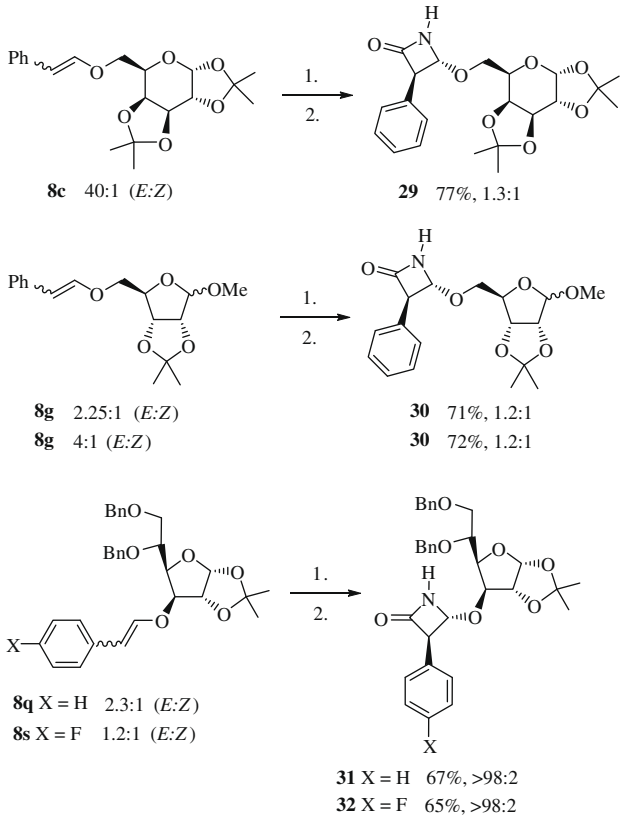
Scheme 4. 2′,5′-Dideoxydisaccharides **25**–**28** prepared by hetero-Diels–Alder of enol ethers **8b**,**c**,**f**, and **g** and 2-formyl-1-malondialdehyde. Reaction conditions: sealed tube, benzene/CH_2Cl_2 (10:1), 70–82 °C, two days.



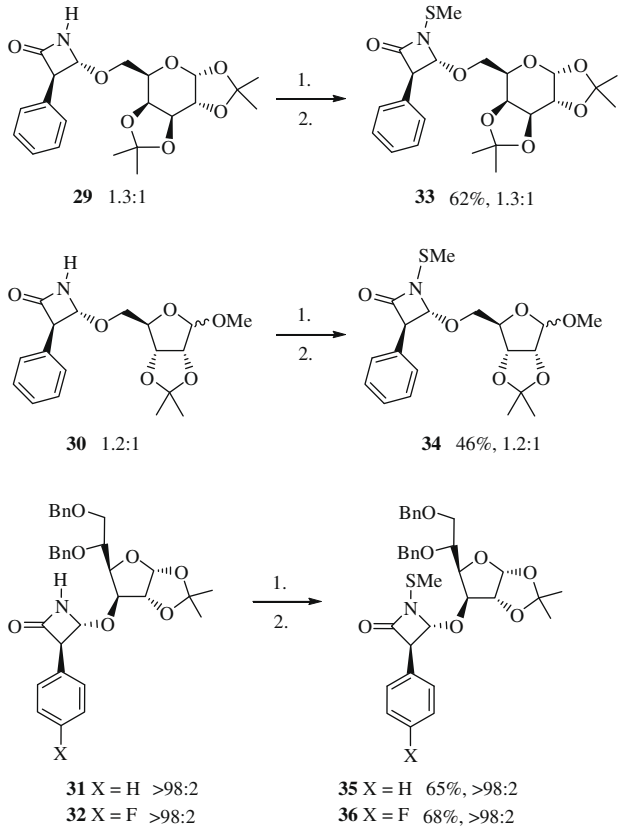
Scheme 5. Proposed explanation for the *endo*-selectivity of the hetero-Diels–Alder cycloadditions of glycosidic enol ethers **8**.

loadditions once again varies depending on the enol ether used. For instance, vinyl ethers of primary hydroxylated carbohydrates (galactose and ribose) led to an almost equimolar mixture of diastereoisomers of β-lactams **29** (1.3:1) and **30** (1.2:1), respectively, while for the enol ether at a secondary hydroxyl position (glucose), β-lactams **31** and **32** were obtained as single diastereomers. We attribute this high stereofacial-differentiation for **31** and **32** to the enhanced steric bias arising from the C4 substituent of the furanoid ring in **8o** and **8q**. This confirms the results of the [4+2] cycloadditions (Scheme 4), in which more steric crowding near the enol oxygen enhances stereoregulation. NMR experiments carried out on the lactam product **31**, and on the diastereomeric mixture of adducts **29** and **30**, confirmed the *trans* stereochemistry of the C3 and C4 ring substituents.[21]

Our study indicates that the stereochemical outcome of the [2+2]-cycloaddition is independent of the geometric structure or *E*/*Z* ratio of the glycosylated enol ethers used. This was further demonstrated in using a different mixture of ethenyl ethers **8g** (*E*/*Z* 4:1), which also gave β-lactam **30** as a 1.2:1 mixture of diastereomers (Scheme 6). This finding, coupled to the exclusive forma-



Scheme 6. Carbohydrated β-lactams **29**–**32** prepared by [2+2] cycloaddition of enol ethers **8c**,**g**,**q**,**s** and chlorosulfonyl isocyanate. Reaction conditions: (1) $ClSO_2NCO$ (3 equiv), Na_2CO_3 (4 equiv), toluene, −70 °C, then −25 °C, 5 h; (2) Red-Al (4 equiv), −70 °C, 45 min, then H_2O, 0 °C, 15 min.



Scheme 7. Synthesis of *N*-(methylthio)-β-lactams **33**–**36**. Reaction conditions: (1) *n*-BuLi, THF, hexanes, −78 to −60 °C, 1 h; (2) $MeSSO_2Me$, −78 °C to rt, 7 h.

tion of only the *trans*-disubstituted β-lactams, suggest a stepwise addition–cyclization reaction mechanism proceeding through a resonance-stabilized zwitterion (Fig. 2).

Earlier studies in our laboratories on N-alkylthiolated β-lactams established that the *N*-organothio substituent is essential for antimicrobial activity of these highly lipophilic molecules.[23] Thus, we wanted to investigate the antibacterial properties of the carbohydrated β-lactams by converting them to the corresponding N-methylthio-substituted derivatives **33–36**. This was done by deprotonation of the *N*-protio precursors **29–32** with *n*-butyllithium, followed by trapping of the lithium amide anion with methyl methanethiolsulfonate (Scheme 7).

2.5. Microbiological testing of lactams 34 and 35

The β-lactams **34** and **35** derived from protected D-(−)-ribose and D-(+)-glucose, respectively, were individually tested for antibacterial activity against methicillin-susceptible and methicillin-resistant strains of *Staphylococcus aureus* Kirby–Bauer well diffusion assays on agar plates for **34** was first done against one MSSA strain and ten MRSA isolates, all of which were β-lactamase producing strains having high resistance to penicillins. The average diameter (from three experiments) of the growth inhibition zones

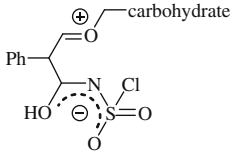


Figure 2. Zwitterion intermediate in the β-lactam formation.

for lactam **34** was 15 mm, with equal effectiveness against MSSA and MRSA. This is a moderate bioactivity although greater than that of the reference drug, penicillin, against MRSA (12 mm) and slightly lower than the activity of another reference drug, vancomycin, against MRSA (18 mm). β-Lactam **35** showed a broth minimum inhibitory concentration (MIC) value of 32 to 64 μg/mL against all the *Staphylococcus* microbes. This likewise represents a moderate, but stronger in vitro activity against MRSA compared to that of penicillin G (MIC >64 μg/mL).[22]

3. Conclusion

In conclusion, we have reported the preparation of glycosidic enol ethers by Julia–Lythgoe–Kocienski coupling of β-glycoside-substituted pyridinylsulfones with aldehydes using solid KOH as a base. Yields and stereoselectivities for this olefination are moderate to excellent depending on the nature of the carbohydrate (primary alcohols vs secondary alcohols) and the steric and electronic properties of the aldehyde. These glycosylated enol ethers serve as convenient starting materials for the synthesis of *O*-linked disaccharides and carbohydrated β-lactams. Facial selectivity of the enol ethers expressed during the cycloadditions is highly dependent on the steric constraints and conformation effects exerted by the carbohydrate moiety.

4. Experimental

4.1. General

All reactions were carried out in an oven-dried (90 °C) or flame-dried glassware under an inert atmosphere with the use of standard techniques for handling air-sensitive materials. All common

reagents and solvents were obtained from commercial suppliers and used without any further purification. Solvents used for the reactions requiring an inert atmosphere were dried before their use:[28] THF and diethyl ether were refluxed over sodium/benzophenone ketyl and distilled immediately prior to use; dichloromethane was refluxed over phosphorus pentoxide (P_4O_{10}) for 24 h and distilled immediately prior to use. Unless otherwise noted, reaction mixtures were magnetically stirred and reactions were monitored by thin layer chromatography (TLC) using on aluminum-backed analytical TLC plates coated with silica gel 60 with F_{254} indicator (Merck Kieselgel 60F254 plates); the chromatograms were visualized under ultraviolet light and/or by staining with a Ce/Mo or DNP (for aldehydes) reagent and subsequent heating. R_f values are reported on silica gel. Flash column chromatography was carried out on J. T. Baker flash chromatography silica gel (40 μm) or on ACROS aluminum oxide, activated, neutral (50–200 micron). Product yields refer to chromatographically and spectroscopically pure compounds, unless otherwise noted. Proton NMR spectra were recorded with the use of an internal deuterium lock at ambient temperature with a Bruker DPX-250 or Varian INOVA-400 spectrometers. Chemical shifts are given in δ units, using the signal at $\delta = 7.27$ for residual $CHCl_3$ in $CDCl_3$ as an internal standard. Chemical shifts are reported in δ units (downfield to $\delta_{TMS} = 0$ ppm), with the signal multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, quint. = quintuplet, m = multiplet, br = broad, app = apparent), coupling constant(s) (J in Hz) and integration area in parentheses. ^{13}C NMR spectra were determined using the signal for residual $CHCl_3$ in $CDCl_3$ at $\delta = 77.16$ as an internal standard. Multiplicities were determined by DEPT, COSY, HMQC, HMBC, and NOESY experiments. Standard pulse sequences were employed for the DEPT experiments. Mass spectra were determined at 70 eV with a Agilent Technologies LC–MSD VL and LC-–MSD TOF for low resolution mass spectra (LRMS), and high resolution mass spectra (HRMS), respectively; the intensities are reported as a percentage relative to the base peak after the corresponding m/z value. ESI Electron spray ionization technique was employed. Infrared spectra were obtained with Thermo Electron Corporation-Nicolet IR 100. Optical rotations were measured with an Autopol® IV polarimeter equipped with a sodium lamp. The concentration c to calculate specific rotation is given in g/100 mL. Melting points were determined on a Mel-Temp II apparatus and are uncorrected.

4.2. Materials

Commercially available D-(−)-ribose, D-(+)-galactose, D-(+)-glucose, BuLi (1.6 m in hexane), and chlorine (g) were used as received. 2-Formyl-1-malondialdehyde was prepared according to the literature procedures.[29]

4.3. General procedure for the preparation of methylthiomethylidene derivatives 2

To a stirring suspension of NaH (1.56 g, 65 mmol; pre-washed with anhydrous hexane to remove the mineral oil dispersant) in THF (60 mL) under argon was added dropwise a solution of the corresponding alcohol **1** (50 mmol) in THF (65 mL). The mixture was then stirred for 45 min. After the mixture was cooled with an ice bath, a solution of chloromethyl methyl sulfide (4.95 mL, 60 mmol) in THF (65 mL) was added slowly followed by NaI (8.99 g, 60 mmol). The ice bath was removed and stirring was continued overnight at room temperature (the product starts to decompose after 12 h of reaction). The reaction was quenched with 5% aqueous NH_4Cl (100 mL), THF was removed under reduced pressure, and the residue was washed with saturated aqueous sodium thiosulfate (2×40 mL) and extracted with diethyl ether (3×40 mL). The extracts were dried over Na_2SO_4 and concentrated in vacuo. The crude was purified by column chromatography on silica gel (Hx/EtOAc 15:1) to afford the corresponding sulfide **2**.

Compound **2a**: Colorless oil in 89% yield. $R_f = 0.34$ (Hx/EtOAc, 8:1); ^1H NMR (400 MHz, $CDCl_3$): δ 1.30 (s, 3H), 1.31 (s, 3H), 1.40 (s, 3H), 1.48 (s, 3H), 2.16 (s, 3H), 3.96 (dd, $J = 8.4, 5.6$, 1H), 4.00–4.13 (m, 2H), 4.22 (td, $J = 5.8, 1.5$, 1H), 4.30 (d, $J = 2.5$, 1H), 4.53 (d, $J = 3.5$, 1H), 4.67 (d, $J = 11.5$, 1H), 4.77 (d, $J = 11.7$, 1H), 5.86 (d, $J = 3.5$, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 13.7 (CH_3), 25.2 (CH_3), 26.0 (CH_3), 26.6 (CH_3), 26.7 (CH_3), 67.4 (CH_2), 72.2 (CH), 74.5 (CH_2), 78.8 (CH), 81.0 (CH), 82.6 (CH), 105.1 (CH), 108.9 (C), 111.7 (C); HRMS (ESI): calcd for $C_{14}H_{25}O_6S$ [M^++H]: 321.1365; found: 321.1357.

Compound **2b**: Colorless oil in 77% yield. $R_f = 0.35$ (Hx/EtOAc, 8:1); ^1H NMR (250 MHz, $CDCl_3$): δ 1.34 (s, 3H), 1.35 (s, 3H), 1.46 (s, 3H), 1.54 (s, 3H), 2.16 (s, 3H), 3.67 (dd, $J = 10.3, 7.1$, 1H), 3.79 (dd, $J = 10.3, 5.2$, 1H), 3.99 (ddd, $J = 7.0, 5.4, 1.8$, 1H), 4.26 (dd, $J = 7.9, 1.9$, 1H), 4.33 (dd, $J = 5.1, 2.4$, 1H), 4.61 (dd, $J = 7.9, 2.5$, 1H), 4.66 (d, $J = 11.5$, 1H), 4.75 (d, $J = 11.5$, 1H), 5.55 (d, $J = 5.1$, 1H); ^{13}C NMR (63 MHz, $CDCl_3$): δ 13.7 (CH_3), 24.3 (CH_3), 24.8 (CH_3), 25.8 (CH_3), 25.9 (CH_3), 66.6 (CH), 66.6 (CH_2), 70.3 (CH), 70.5 (CH), 71.1 (CH), 75.4 (CH_2), 96.2 (CH), 108.4 (C), 109.1 (C); HRMS (ESI): calcd for $C_{14}H_{25}O_6S$ [M^++H]: 321.1365; found: 321.1363.

Compound **2c**: Colorless oil in 72% yield. $R_f = 0.45$ (Hx/EtOAc, 8:1); ^1H NMR (250 MHz, $CDCl_3$): δ 1.33 (s, 3H), 1.49 (s, 3H), 2.16 (s, 3H), 3.34 (s, 3H), 3.52 (dd, $J = 9.7, 8.1$, 1H), 3.60 (dd, $J = 9.8, 7.5$, 1H), 4.33 (td, $J = 7.0, 0.6$, 1H), 4.59 (d, $J = 6.0$, 1H), 4.66–4.69 (m with s at 4.68, 3H), 4.98 (s, 1H); ^{13}C NMR (63 MHz, $CDCl_3$): δ 13.8 (CH_3), 24.8 (CH_3), 26.3 (CH_3), 54.7 (CH_3), 68.7 (CH_2), 75.4 (CH_2), 82.0 (CH), 84.9 (CH), 85.0 (CH), 109.1 (CH), 112.2 (C); HRMS (ESI): calcd for $C_{11}H_{21}O_5S$ [M^++H]: 265.1104; found: 265.1110.

4.3.1. Synthesis of diol 6[30]

Diacetonide **2a** (6.30 g, 19.7 mmol) was dissolved in a mixture of CH_2Cl_2/isopropyl alcohol (4:1, 100 mL) and then $NaHSO_4$?SiO_2 (1.97 g) was added at room temperature.[31] The reaction mixture was stirred for two days. The mixture was then filtered, and concentrated under vacuum. The crude was chromatographed on a silica gel column (CH_2Cl_2/EtOAc 1:1) to give diol **6** (4.74 g, 16.94 mmol, 86%) as a colorless oil. $R_f = 0.26$ (CH_2Cl_2/EtOAc 1:1); ^1H NMR (400 MHz, $CDCl_3$): δ 1.32 (s, 3H), 1.50 (s, 3H), 2.24 (s, 3H), 2.29 (br s, 1H, CHO*H*), 2.98 (d, $J = 5.3$, 1H, CH_2O*H*), 3.70–3.79 (m, 1H), 3.83–4.00 (m, 2H), 4.15 (dd, $J = 8.1, 2.9$, 1H), 4.26 (d, $J = 3.0$, 1H), 4.57 (d, $J = 3.8$, 1H), 4.67 (d, $J = 11.8$, 1H), 4.85 (d, $J = 11.8$, 1H), 5.91 (d, $J = 3.8$, 1H); ^{13}C NMR (63 MHz, $CDCl_3$): δ 14.7 (CH_3), 26.5 (CH_3), 26.9 (CH_3), 64.4 (CH_2), 69.0 (CH), 75.5 (CH_2), 79.9 (CH), 80.2 (CH), 82.8 (CH), 105.4 (CH), 112.1 (C); HRMS (ESI): calcd for $C_{11}H_{21}O_6S$ [M^++H]: 281.1053; found: 281.1047.

4.3.2. Synthesis of compound 7

Over a stirred suspension of NaH (591 mg, 24.6 mmol; washed with hexane) in THF (40 mL) under argon was added a solution of diol **6** (2.3 g, 8.2 mmol) in THF (30 mL). The mixture was then stirred for 45 min. Then, a solution of benzyl bromide (4.92 mL, 41.0 mmol, 7.03 g) in THF (20 mL) was added to the mixture. Stirring was continued at room temperature overnight. The reaction was quenched with NH_4Cl (40 mL), THF was removed under reduced pressure, and the residue was extracted with CH_2Cl_2 (2×40 mL) and with ether (1×40 mL). The extracts were dried over Na_2SO_4 and concentrated in vacuo. The crude product mixture was chromatographed on a silica gel column (Hx/EtOAc 5:1) to give compound **7** (3.52 g, 7.64 mmol, 93%) as a yellow oil. $R_f = 0.44$ (Hx/EtOAc 4:1); ^1H NMR (250 MHz, $CDCl_3$): δ 1.33 (s, 3H), 1.50 (s, 3H), 2.12 (s, 3H), 3.72 (dd, $J = 10.8, 5.8$, 1H), 3.93–4.03 (m, 2H), 4.25 (d, $J = 3.3$, 1H), 4.34 (dd, $J = 9.3, 3.3$, 1H), 4.55–4.69 (m with s at 4.60, 6H), 4.88 (d, $J = 11.3$, 1H), 5.90 (d, $J = 3.8$,

1H), 7.23–7.40 (m, 10H); ^{13}C NMR (63 MHz, $CDCl_3$): δ 14.4 (CH_3), 26.1 (CH_3), 26.5 (CH_3), 70.6 (CH_2), 71.8 (CH_2), 73.1 (CH_2), 75.0 (CH_2), 75.1 (CH), 78.5 (CH), 80.4 (CH), 82.1 (CH), 104.7 (CH), 111.6 (C), 127.2 (CH), 127.3 (CH), 127.4 (5 × CH), 128.1 (3 × CH), 138.3 (C), 138.3 (C); HRMS (ESI): calcd for $C_{27}H_{33}O_6S$ [M^++H]: 485.1989; found: 485.1996.

4.4. General procedure for the preparation of chloromethyl derivatives 3

Into a solution of sulfide **2a–c** or **7** (30 mmol) in CCl_4 (100 mL) was slowly bubbled Cl_2 gas for 1 min at room temperature. After this period, CCl_4 was removed under reduced pressure. The residue was washed with water (40 mL) and extracted with CH_2Cl_2 (3 × 40 mL). The extracts were dried over Na_2SO_4 and concentrated in vacuo. Due to the instability of chloromethyl ethers, the crude product **3** was used for the next step without further purification. NMR of the crude mixture show yields estimated to be over 95%.

Compound **3d**: R_f = 0.50 (Hx/EtOAc, 4:1); ^{1}H NMR (250 MHz, $CDCl_3$): δ 1.34 (s, 3H), 1.51 (s, 3H), 2.12 (s, 3H), 3.70 (dd, J = 11.0, 5.5, 1H), 3.87–3.96 (m, 2H), 4.35 (s, 1H), 4.36 (dd, J = 10.5, 2.8, 1H), 4.57 (d, J = 11.4, 1H), 4.61 (s, 2H), 4.72 (d, J = 3.8, 1H), 4.85 (d, J = 11.4, 1H), 5.32 (d, J = 5.9, 1H), 5.43 (d, J = 5.9, 1H), 5.90 (d, J = 3.8, 1H), 7.29–7.40 (m, 10H); ^{13}C NMR (63 MHz, $CDCl_3$): δ 26.2 (CH_3), 26.6 (CH_3), 70.4 (CH_2), 72.0 (CH_2), 73.3 (CH_2), 74.7 (CH), 78.1 (CH), 81.5 (CH_2), 82.2 (CH), 82.4 (CH), 104.8 (CH), 112.0 (C), 127.4 (CH), 127.5 (2 × CH), 127.6 (CH), 127.8 (2 × CH), 128.2 (2 × CH), 128.3 (2 × CH), 138.2 (C), 138.3 (C).

4.5. General procedure for the preparation of (2-pyridinyl)thiomethyl derivatives 4

To a stirred suspension of NaH (0.93 g, 39 mmol; pre-washed with hexane) in THF (80 mL) under argon was added a solution of 2-mercaptopyridine (4.00 g, 36 mmol) in THF (80 mL). The mixture was then stirred for 45 min. After the mixture was cooled with an ice bath, there was added dropwise a solution of the chloromethyl glycoside **3** (30 mmol) and NaI (5.39 g, 36 mmol) in THF (80 mL). The ice bath was then removed and stirring was continued at room temperature for overnight. The reaction was quenched with NH_4Cl (100 mL), THF was removed under reduced pressure, and the residue washed with saturated aqueous sodium thiosulfate (2 × 40 mL) and extracted with ether (3 × 40 mL). The extracts were dried over Na_2SO_4 and concentrated in vacuo. The crude was chromatographed on a silica gel column (Hx/EtOAc 5:1) to give the corresponding pyridinylthiomethyl derivative **4**.

Compound **4b**: Orange oil in 73% yield after two steps. R_f = 0.27 (Hx/EtOAc, 4:1); ^{1}H NMR (250 MHz, $CDCl_3$): δ 1.31 (s, 3H), 1.32 (s, 3H), 1.44 (s, 3H), 1.51 (s, 3H), 3.75 (dd, J = 10.4, 7.1, 1H), 3.83 (dd, J = 10.4, 5.5, 1H), 4.02 (app td, J = 6.2, 1.5, 1H), 4.20 (dd, J = 7.9, 1.6, 1H), 4.30 (dd, J = 5.1, 2.4, 1H), 4.39 (d, J = 3.0, 1H), 4.58 (dd, J = 7.9, 2.3, 1H), 5.36 (d, J = 11.5, 1H), 5.49 (d, J = 11.5, 1H), 5.53 (d, J = 5.4, 1H), 7.00–7.05 (m, 1H), 7.33 (d, J = 8.1, 1H), 7.51 (td, J = 7.8, 1.6, 1H), 8.45 (ddd, J = 4.9, 2.0, 1.0, 1H); ^{13}C NMR (63 MHz, $CDCl_3$): δ 24.2 (CH_3), 24.7 (CH_3), 25.8 (CH_3), 25.8 (CH_3), 66.3 (CH), 67.4 (CH_2), 70.3 (CH), 70.4 (CH), 70.8 (CH), 72.1 (CH_2), 96.1 (CH), 108.3 (C), 109.0 (C), 120.0 (CH), 122.5 (CH), 136.2 (CH), 149.2 (CH), 157.8 (C); HRMS (ESI): calcd for $C_{18}H_{26}NO_6S$ [M^++H]: 384.1473; found: 384.1471.

Compound **4c**: Orange oil in 86% yield after two steps. R_f = 0.35 (Hx/EtOAc, 2:1); ^{1}H NMR (250 MHz, $CDCl_3$): δ 1.27 (s, 3H), 1.45 (s, 3H), 3.24 (s, 3H), 3.56 (dd, J = 9.7, 8.1, 1H), 3.65 (dd, J = 9.7, 6.4, 1H), 4.32 (app t, J = 7.1, 2H), 4.54 (d, J = 6.0, 1H), 4.61 (d, J = 4.9, 1H), 4.93 (s, 1H), 5.40 (s, 2H), 7.03 (ddd, J = 7.4, 4.9, 1.1, 1H), 7.30 (d, J = 7.9, 1H), 7.52 (td, J = 7.4, 1.9, 1H), 8.44 (ddd, J = 4.9, 1.9, 0.8, 1H); ^{13}C NMR (63 MHz, $CDCl_3$): δ 24.5 (CH_3), 26.0 (CH_3), 54.3 (OCH_3), 69.3 (CH_2), 71.6 (CH_2), 81.6 (CH), 84.3 (CH), 84.7 (CH), 108.8 (CH), 111.8 (C), 119.8 (CH), 122.3 (CH), 136.0 (CH), 149.0 (CH), 157.2 (C); HRMS (ESI): calcd for $C_{15}H_{22}NO_5S$ [M^++H]: 328.1212; found: 328.1216.

Compound **4d**: Colorless oil in 86% yield after two steps. R_f = 0.25 (Hx/EtOAc, 4:1); ^{1}H NMR (250 MHz, $CDCl_3$): δ 1.34 (s, 3H), 1.51 (s, 3H), 3.69 (dd, J = 10.6, 5.6, 1H), 3.91 (dd, J = 10.6, 2.1, 1H), 3.96–4.02 (m, 1H), 4.34 (dd, J = 9.1, 2.9, 1H), 4.40 (d, J = 3.3, 1H), 4.47 (d, J = 11.3, 1H), 4.60 (s, 2H), 4.74 (d, J = 3.3, 1H), 4.77 (d, J = 4.5, 1H), 5.42 (d, J = 11.5, 1H), 5.52 (d, J = 11.5, 1H), 5.89 (d, J = 3.8, 1H), 7.13 (m, 1H), 7.26–7.39 (m, 11H), 7.58–7.67 (m, 1H), 8.48 (dddd, J = 10.8, 4.9, 1.8, 0.9, 1H); ^{13}C NMR (63 MHz, $CDCl_3$): δ 26.1 (CH_3), 26.5 (CH_3), 70.1 (CH_2), 70.8 (CH_2), 72.1 (CH_2), 73.1 (CH_2), 74.9 (CH), 78.2 (CH), 80.4 (CH), 81.7 (CH), 104.7 (CH), 111.5 (C), 120.1 (CH), 122.4 (CH), 127.2 (CH), 127.3 (CH), 127.5 (2 × CH), 128.0 (3 × CH), 128.1 (3 × CH), 136.2 (CH), 138.3 (C), 138.5 (C), 149.3 (CH), 156.4 (C); HRMS (ESI): calcd for $C_{31}H_{34}NO_6S$ [M^++H]: 548.2097; found: 548.2103.

4.6. General procedures for the preparation of (2-pyridinyl)sulfonylmethylidene derivatives 5

Method A: To a cooled solution of sulfide **4** (20 mmol) in CH_2Cl_2 (300 mL) at 0 °C were added 3-chloroperoxybenzoic acid (70%, 14.8 g, 60 mmol) and then sodium phosphate dibasic (21.3 g, 150 mmol). The ice bath was removed and stirring was continued at room temperature for 5 h. The reaction mixture was filtered and concentrated in vacuo. The crude was purified by flash column chromatography (Hx/EtOAc 3:1 and then Hx/EtOAc 3:2) to give the corresponding sulfone **5**.

Method B:[4h] To a solution of the sulfide **4** (20 mmol) in methanol (180 mL) at 0 °C was added sodium tungstate dihydrate (0.66 g, 2.0 mmol), followed by slow addition of 30% aqueous H_2O_2 (20.6 mL, 0.2 mol). The reaction mixture was allowed to warm to room temperature and was stirred for 8 h. The reaction mixture was then diluted with CH_2Cl_2 (180 mL) and a solution of 10% aqueous $NaHSO_3$ was added. The biphasic mixture was stirred for 15 min and the layers were separated. The aqueous layer was washed with CH_2Cl_2 (2 × 70 mL) and the combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The crude was purified by column chromatography (Hx/EtOAc 3:1 and then Hx/EtOAc 3:2) to give the corresponding sulfone **5**.

Compound **5a**: White solid in 86% yield. R_f = 0.35 (Hx/EtOAc, 4:3); ^{1}H NMR (250 MHz, $CDCl_3$): δ 1.28 (s, 3H), 1.32 (s, 3H), 1.41 (s, 3H), 1.46 (s, 3H), 3.89 (app d, J = 4.9, 2H), 4.00–4.13 (m, 2H), 4.41 (d, J = 1.7, 1H), 4.50 (d, J = 3.5, 1H), 5.06 (d, J = 12.8, 1H), 5.19 (d, J = 12.8, 1H), 5.76 (d, J = 3.5, 1H), 7.64 (ddd, J = 7.6, 4.6, 1.0, 1H), 8.05 (td, J = 7.7, 1.6, 1H), 8.20 (dt, J = 7.9, 0.6, 1H), 8.80 (dt, J = 3.8, 0.8, 1H); ^{13}C NMR (63 MHz, $CDCl_3$): δ 24.8 (CH_3), 25.8 (CH_3), 26.3 (2 × CH_3), 66.6 (CH_2), 72.0 (CH), 80.4 (CH), 81.6 (CH_2), 82.6 (CH), 84.6 (CH), 104.6 (CH), 108.8 (C), 111.6 (C), 123.1 (CH), 127.5 (CH), 137.9 (CH), 150.1 (CH), 155.3 (C); HRMS (ESI): calcd for $C_{18}H_{26}NO_8S$ [M^++H]: 416.1371; found: 416.1369.

Compound **5b**: Colorless oil in 77% yield. R_f = 0.27 (Hx/EtOAc, 3:2); ^{1}H NMR (250 MHz, $CDCl_3$): δ 1.31 (s, 6H), 1.42 (s, 3H), 1.46 (s, 3H), 3.85–3.94 (m, 2H), 3.99–4.05 (m, 1H), 4.12 (dd, J = 7.8, 1.5, 1H), 4.29 (dd, J = 5.1, 2.5, 1H), 4.57 (dd, J = 7.9, 2.5, 1H), 4.94 (d, J = 12.6, 1H), 5.07 (d, J = 12.6, 1H), 5.49 (d, J = 5.1, 1H), 7.56 (ddd, J = 7.7, 4.7, 1.1, 1H), 7.97 (td, J = 7.7, 1.7, 1H), 8.15 (app d, J = 7.9, 1H), 8.78 (ddd, J = 4.6, 1.6, 0.8, 1H); ^{13}C NMR (63 MHz, $CDCl_3$): δ 23.9 (CH_3), 24.4 (CH_3), 25.4 (2 × CH_3), 66.4 (CH), 69.8 (CH), 70.0 (CH), 70.2 (CH), 71.7 (CH_2), 83.0 (CH_2), 95.6 (CH), 108.1 (C), 108.9 (C), 123.4 (CH), 127.3 (CH), 137.8 (CH), 149.9 (CH), 155.1 (C); HRMS (ESI): calcd for $C_{18}H_{26}NO_8S$ [M^++H]: 416.1371; found: 416.1365.

Compound **5c**: White solid in 78% yield. R_f = 0.12 (Hx/EtOAc, 2:1); ^{1}H NMR (250 MHz, $CDCl_3$): δ 1.21 (s, 3H), 1.37 (s, 3H), 3.21 (s, 3H), 3.75 (dd, J = 10.0, 7.9, 1H), 3.81 (dd, J = 10.0, 6.6, 1H), 4.14 (app t, J = 7.1, 1H), 4.46 (d, J = 7.0, 1H), 4.49 (d, J = 6.5, 1H), 4.85 (s, 1H), 4.91 (d, J = 3.3, 2H), 7.54 (ddd, J = 7.6, 4.7, 1.1, 1H), 7.94 (td, J = 7.7, 1.6, 1H), 8.08 (d, J = 7.9, 1H), 8.71 (ddd, J = 4.7, 1.6, 0.8, 1H); ^{13}C NMR (63 MHz, $CDCl_3$): δ 24.6 (CH_3), 26.1 (CH_3), 54.7 (CH_3), 73.7 (CH_2), 81.3 (CH), 82.9 (CH_2), 84.2 (CH), 84.7 (CH), 109.1 (CH), 112.2 (C), 123.3 (CH), 127.5 (CH), 138.0 (CH), 150.2 (CH), 155.6 (C); HRMS (ESI): calcd for $C_{15}H_{22}NO_7S$ [M^++H]: 360.1110; found: 360.1115.

Compound **5d**: White solid in 84% yield. R_f = 0.23 (Hx/EtOAc, 2:1); ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.29 (s, 3H), 1.47 (s, 3H), 3.65 (dd, J = 10.5, 4.8, 1H), 3.77–3.83 (m, 1H), 3.89 (dd, J = 10.6, 1.4, 1H), 4.28–4.32 (m with s at 4.32, 2H), 4.46 (d, J = 11.5, 1H), 4.56 (s, 2H), 4.58 (d, J = 4.0, 1H), 4.80 (d, J = 11.3, 1H), 4.82 (d, J = 12.5, 1H), 4.98 (d, J = 12.3, 1H), 5.75 (d, J = 3.8, 1H), 7.28–7.36 (m, 10H), 7.51 (ddd, J = 7.3, 4.8, 0.5, 1H), 7.89 (td, J = 7.8, 1.3, 1H), 8.06 (d, J = 7.8, 1H), 8.71 (d, J = 4.3, 1H); ^{13}C NMR (63 MHz, $CDCl_3$): δ 25.9 (CH_3), 26.3 (CH_3), 69.6 (CH_2), 71.2 (CH_2), 72.8 (CH_2), 74.6 (CH), 78.0 (CH), 81.8 (CH_2), 82.1 (CH), 84.7 (CH), 104.2 (CH), 111.5 (C), 122.7 (CH), 127.1 (CH), 127.1 (2 × CH), 127.3 (CH), 127.4 (2 × CH), 127.9 (2 × CH), 128.0 (2 × CH), 137.8 (C), 137.9 (CH+C), 149.9 (CH), 155.3 (C); HRMS (ESI): calcd for $C_{31}H_{34}NO_8S$ [M^++H]: 580.1995; found: 580.1999.

4.7. General procedure for the preparation of enol ethers 8

To a stirred solution of sulfone **5** (1.0 mmol) and tetrabutylammonium bromide (65 mg, 0.2 mmol) in THF (30 mL) at room temperature was added the corresponding aldehyde (1.8 mmol). After 10 min, pulverized potassium hydroxide (0.85 g, 15.0 mmol) was added at room temperature. The solution was stirred for 24 h and then THF was removed under reduced pressure. The crude was washed with water (40 mL) and extracted with ethyl acetate (3 × 30 mL). The organic layers were combined and dried over Na_2SO_4 and concentrated in vacuo. The crude was purified by column chromatography (Al_2O_3) (Hx and then Hx/EtOAc 15:1 or Hx/CH_2Cl_2 3:2) to give the corresponding enol ether **8**. Enol ethers **8** are relatively unstable on SiO_2.

Compound **8a**: Pale yellow oil in 63% yield and as a 75:25 mixture of *E*/*Z* diastereomers. R_f = 0.48 (Hx/EtOAc, 6:1); ^{1}H NMR (250 MHz, $CDCl_3$): δ 1.24 (s, 3H), 1.25 (s, 3H), 1.36 (s, 3H), 1.45 (s, 3H), 3.96 (dd, J = 8.6, 5.3, 1H), 4.04 (dd, J = 8.6, 6.0, 1H), 4.12 (dd, J = 8.1, 2.9, 1H), 4.23–4.32 (m, 1H), 4.36 (d, J = 2.9, 1H), 4.57 (d, J = 3.7, 1H), 5.84 (d, J = 3.8, 1H), 5.92 (d, J = 13.0, 1H), 6.86 (d, J = 13.0, 1H), 7.12–7.21 (m, 5H); ^{13}C NMR (63 MHz, $CDCl_3$): δ 25.2 (CH_3), 26.1 (CH_3), 26.6 (CH_3), 26.8 (CH_3), 67.2 (CH_2), 71.9 (CH), 80.5 (CH), 82.0 (CH), 82.3 (CH), 105.0 (CH), 108.6 (CH), 109.2 (C), 112.0 (C), 125.1 (CH), 128.2 (2 × CH), 128.4 (2 × CH), 135.8 (C), 146.0 (CH). Resolved signals for the minor isomer: ^{1}H NMR (250 MHz, $CDCl_3$): δ 1.23 (s, 3H), 3.97 (dd, J = 8.5, 5.1, 1H), 4.56 (d, J = 3.6, 1H), 5.25 (d, J = 7.0, 1H), 5.89 (d, J = 3.7, 1H), 6.19 (d, J = 7.0, 1H), 7.42 (d, J = 7.6, 2H); ^{13}C NMR (63 MHz, $CDCl_3$): δ 25.1 (CH_3), 67.3 (CH_2), 72.0 (CH), 80.7 (CH), 105.1 (CH), 109.3 (C), 112.1 (C), 126.0 (CH), 128.5 (2 × CH), 135.5 (C), 144.8 (CH); HRMS (ESI) of the mixture: calcd for $C_{20}H_{26}O_6Na$ [M^++Na]: 385.1620; found: 385.1614.

Compound **8b**: Colorless oil in 54% yield and as a 75:25 mixture of *E*/*Z* diastereomers. R_f = 0.39 (Hx/EtOAc, 6:1); ^{1}H NMR (250 MHz, $CDCl_3$): δ 1.25 (s, 6H), 1.36 (s, 3H), 1.45 (s, 3H), 3.96 (dd, J = 8.7, 5.2, 1H), 4.04 (dd, J = 8.7, 6.0, 1H), 4.11 (dd, J = 8.1, 2.8, 1H), 4.21–4.31 (m, 1H), 4.34 (d, J = 2.8, 1H), 4.56 (d, J = 3.6, 1H), 5.84 (d, J = 3.6, 1H), 5.89 (d, J = 12.8, 1H), 6.78 (d, J = 12.8, 1H), 6.84–7.42 (m, 4H); ^{13}C NMR (63 MHz, $CDCl_3$): δ 25.2 (CH_3), 26.1 (CH_3), 26.6 (CH_3), 26.8 (CH_3), 67.2 (CH_2), 71.9 (CH), 80.5 (CH), 82.1 (CH), 82.4 (CH), 105.1 (CH), 107.7 (CH), 109.3 (C), 112.1 (C), 115.4 (d, J = 21.6, 2 × CH), 126.5 (d, J = 7.8, 2 × CH), 130.2 (d, J = 8.3, C), 145.8 (d, J = 1.4, CH), the fluorinated carbon was not resolved. Resolved signals for the minor isomer: ^{1}H NMR (250 MHz, $CDCl_3$): δ 5.23 (d, J = 6.9, 1H), 5.88 (d, J = 3.9, 1H), 6.18 (d, J = 7.0, 1H); HRMS (ESI) of the mixture: calcd for $C_{20}H_{25}O_6FNa$ [M^++Na]: 403.1526; found: 403.1532.

Compound **8c**: White solid in 71% yield and as a 96:4 mixture of *E*/*Z* diastereomers. R_f = 0.47 (Hx/EtOAc, 6:1); ^{1}H NMR (250 MHz, $CDCl_3$): δ 1.35 (s, 3H), 1.37 (s, 3H), 1.49 (s, 3H), 1.55 (s, 3H), 3.93–4.15 (m with d at 4.03, J = 3.5, and d at 4.10, J = 6.8, 3H), 4.32 (dd, J = 7.9, 1.7, 1H), 4.36 (dd, J = 5.0, 2.5, 1H), 4.66 (dd, J = 7.9, 2.4, 1H), 5.58 (d, J = 4.9, 1H), 5.89 (d, J = 13.0, 1H), 7.04 (d, J = 13.0, 1H), 7.13–7.26 (m with s at 7.23, 5H); ^{13}C NMR (63 MHz, $CDCl_3$): δ 24.4 (CH_3), 24.9 (CH_3), 25.9 (CH_3), 26.0 (CH_3), 66.3 (CH), 68.3 (CH_2), 70.5 (CH), 70.6 (CH), 71.0 (CH), 96.3 (CH), 106.3 (CH), 108.7 (C), 109.5 (C), 125.1 (2 × CH), 125.6 (CH), 128.5 (2 × CH), 136.2 (C), 147.7 (CH). Resolved signals for the minor isomer: ^{1}H NMR (250 MHz, $CDCl_3$): δ 5.26 (d, J = 7.1, 1H), 6.26 (d, J = 7.1, 1H); HRMS (ESI) of the mixture: calcd for $C_{20}H_{26}O_6Na$ [M^++Na]: 385.1620; found: 385.1622.

Compound **8d**: Colorless oil in 91% yield and as a 89:11 mixture of *E*/*Z* diastereomers. R_f = 0.37 (Hx/EtOAc, 6:1); ^{1}H NMR (250 MHz, $CDCl_3$): δ 1.35 (s, 3H), 1.37 (s, 3H), 1.48 (s, 3H), 1.55 (s, 3H), 3.79 (s, 3H), 3.96–4.13 (m, 3H), 4.31 (dd, J = 8.0, 1.8, 1H), 4.35 (dd, J = 5.1, 2.5, 1H), 4.65 (dd, J = 7.9, 2.5, 1H), 5.57 (d, J = 5.1, 1H), 5.86 (d, J = 13.0, 1H), 6.82 (d, J = 8.7, 2H), 6.92 (d, J = 13.0, 1H), 7.15 (d, J = 8.7, 2H); ^{13}C NMR (63 MHz, $CDCl_3$): δ 24.4 (CH_3), 24.8 (CH_3), 25.9 (CH_3), 26.0 (CH_3), 55.2 (CH_3), 66.2 (CH), 68.2 (CH_2), 70.4 (CH), 70.6 (CH), 70.9 (CH), 96.3 (CH), 105.9 (CH), 108.6 (C), 109.4 (C), 114.0 (2 × CH), 126.1 (2 × CH), 128.8 (C), 146.4 (CH), 157.8 (C). Resolved signals for the minor isomer: ^{1}H NMR (250 MHz, $CDCl_3$): δ 3.80 (s, 3H), 5.21 (d, J = 7.0, 1H), 6.18 (d, J = 7.0, 1H), 6.83 (d, J = 8.8, 2H), 7.54 (d, J = 8.8, 2H); ^{13}C NMR (63 MHz, $CDCl_3$): δ 24.3 (CH_3), 55.1 (CH_3), 66.8 (CH), 70.5 (CH), 70.8 (CH), 96.2 (CH), 105.7 (CH), 109.3 (C), 113.5 (2 × CH), 128.7 (C), 144.8 (CH), 157.5 (C); HRMS (ESI) of the mixture: calcd for $C_{21}H_{28}O_7Na$ [M^++Na]: 415.1725; found: 415.1717.

Compound **8e**: Colorless oil in 78% yield and as a 89:11 mixture of *E*/*Z* diastereomers. R_f = 0.28 (Hx/EtOAc, 6:1); 0.18 (Hx/CH_2Cl_2, 6:1); ^{1}H NMR (250 MHz, $CDCl_3$): δ 1.35 (s, 3H), 1.38 (s, 3H), 1.49 (s, 3H), 1.56 (s, 3H), 3.84 (s, 3H), 3.98–4.16 (m, 3H), 4.33 (dd, J = 7.9, 1.7, 1H), 4.36 (dd, J = 5.2, 2.5, 1H), 4.66 (dd, J = 7.9, 2.5, 1H), 5.58 (d, J = 4.9, 1H), 6.11 (d, J = 13.0, 1H), 6.83–6.91 (m, 2H), 7.01–7.18 (m with d at 7.15, J = 12.9, 2H), 7.24 (dd, J = 7.6, 1.4, 1H); ^{13}C NMR (63 MHz, $CDCl_3$): δ 24.3 (CH_3), 24.8 (CH_3), 25.8 (CH_3), 25.9 (CH_3), 55.2 (CH_3), 66.2 (CH), 67.9 (CH_2), 70.4 (CH), 70.5 (CH), 70.9 (CH), 96.2 (CH), 101.8 (CH), 108.6 (C), 109.3 (C), 110.5 (CH), 120.5 (CH), 125.0 (C), 126.0 (CH), 126.4 (CH), 148.4 (CH), 155.8 (C). Resolved signals for the minor isomer: ^{1}H NMR (250 MHz, $CDCl_3$): δ 3.82 (s, 3H), 4.63 (dd, J = 7.6, 2.5, 1H), 5.56 (d, J = 4.9, 1H), 5.69 (d, J = 7.1, 1H), 6.31 (d, J = 7.1, 1H); ^{13}C NMR (63 MHz, $CDCl_3$): δ 24.2 (CH_3), 55.3 (CH_3), 66.6 (CH), 70.7 (CH), 71.6 (CH), 96.1 (CH), 99.1 (CH), 109.2 (C), 110.0 (CH), 120.3 (CH), 126.6 (CH), 146.4 (CH); HRMS (ESI) of the mixture: calcd for $C_{21}H_{28}O_7Na$ [M^++Na]: 415.1725; found: 415.1719.

Compound **8f**: Colorless oil in 40% yield and as a 93:7 mixture of *E*/*Z* diastereomers. R_f = 0.34 (Hx/EtOAc, 6:1); ^{1}H NMR (250 MHz, $CDCl_3$): δ 1.34 (s, 3H), 1.37 (s, 3H), 1.48 (s, 3H), 1.55 (s, 3H), 3.94–4.14 (m, 3H), 4.30 (dd, J = 7.9, 1.8, 1H), 4.35 (dd, J = 5.1, 2.5, 1H), 4.65 (dd, J = 7.9, 2.5, 1H), 5.57 (d, J = 5.0, 1H), 5.85 (d, J = 13.0, 1H), 6.91–6.98 (m with d at 6.95, J = 13.0, 3H), 7.16 (dd, J = 8.7, 5.4, 2H); ^{13}C NMR (63 MHz, $CDCl_3$): δ 24.3 (CH_3), 24.8 (CH_3), 25.9 (CH_3), 25.9 (CH_3), 66.2 (CH), 68.3 (CH_2), 70.4 (CH), 70.5 (CH), 70.9 (CH), 96.2 (CH), 105.2 (CH), 108.7 (C), 109.4 (C), 115.4 (d, J = 21.6, 2 × CH), 126.4 (d, J = 7.4, 2 × CH), 132.2 (d,

J = 3.2, C), 147.5 (d, J = 1.4, CH), 161.1 (d, J = 244.1, C). Resolved signals for the minor isomer: ^{1}H NMR (250 MHz, $CDCl_3$): δ 1.53 (s, 3H), 5.22 (d, J = 7.0, 1H), 6.23 (d, J = 7.0, 1H), 7.56 (dd, J = 8.8, 5.7, 2H); ^{13}C NMR (63 MHz, $CDCl_3$): δ 24.3 (CH_3), 24.8 (CH_3), 66.8 (CH), 70.5 (CH), 70.8 (CH), 71.9 (CH), 96.2 (CH), 105.0 (CH), 114.8 (d, J = 21.1, 2 × CH), 129.7 (d, J = 7.4, 2 × CH), 146.0 (d, J = 1.4, CH), 161.0 (d, J = 212.8, C); HRMS (ESI) of the mixture: calcd for $C_{20}H_{25}O_6FNa$ [M^++Na]: 381.1706; found: 381.1714.

Compound **8g**: Colorless oil in 72% yield and as a 96:4 mixture of *E*/*Z* diastereomers. R_f = 0.38 (Hx/EtOAc, 6:1); ^{1}H NMR (250 MHz, $CDCl_3$): δ 1.35 (s, 3H), 1.51 (s, 3H), 3.37 (s, 3H), 3.82 (dd, J = 9.9, 8.1, 1H), 3.89 (dd, J = 9.9, 6.8, 1H), 4.46 (app t, J = 7.4, 1H), 4.63 (d, J = 6.0, 1H), 4.74 (d, J = 5.9, 1H), 5.02 (s, 1H), 5.87 (d, J = 13.0, 1H), 7.01 (d, J = 13.0, 1H), 7.23 (s, 2H), 7.24 (s, 3H); ^{13}C NMR (63 MHz, $CDCl_3$): δ 24.9 (CH_3), 26.4 (CH_3), 54.9 (CH_3), 70.1 (CH_2), 81.8 (CH), 84.4 (CH), 85.0 (CH), 106.5 (CH), 109.3 (CH), 112.6 (C), 125.1 (2 × CH), 125.8 (CH), 128.5 (2 × CH), 136.0 (C), 147.4 (CH). Resolved signals for the minor isomer: ^{1}H NMR (250 MHz, $CDCl_3$): δ 5.27 (d, J = 7.0, 1H), 6.20 (d, J = 7.0, 1H); HRMS (ESI) of the mixture: calcd for $C_{17}H_{22}O_5Na$ [M^++Na]: 329.1359; found: 329.1366.

Compound **8h**: Colorless oil in 88% yield and as a 78:22 mixture of *E*/*Z* diastereomers. R_f = 0.33 (Hx/EtOAc, 6:1); ^{1}H NMR (250 MHz, $CDCl_3$): δ 1.34 (s, 3H), 1.51 (s, 3H), 3.36 (s, 3H), 3.76–3.93 (m with s at 3.79, 5H), 4.45 (app t, J = 7.4, 1H), 4.62 (d, J = 5.8, 1H), 4.73 (d, J = 5.7, 1H), 5.02 (s, 1H), 5.84 (d, J = 12.9, 1H), 6.82 (d, J = 8.8, 2H), 6.89 (d, J = 12.9, 1H), 7.15 (d, J = 8.8, 2H); ^{13}C NMR (63 MHz, $CDCl_3$): δ 24.9 (CH_3), 26.3 (CH_3), 54.8 (CH_3), 55.2 (CH_3), 70.1 (CH_2), 81.8 (CH), 84.4 (CH), 85.0 (CH), 106.1 (CH), 109.3 (CH), 112.5 (C), 114.0 (2 × CH), 126.1 (2 × CH), 128.5 (C), 146.0 (CH), 157.9 (C). Resolved signals for the minor isomer: ^{1}H NMR (250 MHz, $CDCl_3$): δ 5.22 (d, J = 7.0, 1H), 6.11 (d, J = 7.0, 1H), 7.55 (d, J = 8.8, 2H); ^{13}C NMR (63 MHz, $CDCl_3$): δ 55.1 (CH_3), 81.6 (CH), 84.7 (CH), 85.1 (CH), 106.0 (CH), 109.4 (CH), 112.4 (C), 113.6 (2 × CH), 128.4 (C), 129.5 (2 × CH), 144.3 (CH); HRMS (ESI) of the mixture: calcd for $C_{18}H_{24}O_6Na$ [M^++Na]: 359.1464; found: 359.1460.

Compound **8i**: Colorless oil in 83% yield and as a 71:29 mixture of *E*/*Z* diastereomers. R_f = 0.35 (Hx/EtOAc, 6:1); ^{1}H NMR (250 MHz, $CDCl_3$): δ 1.34 (s, 3H), 1.51 (s, 3H), 3.36 (s, 3H), 3.85 (s, 3H), 3.87–3.94 (m, 2H), 4.43–4.51 (m, 1H), 4.63 (d, J = 5.9, 1H), 4.75 (d, J = 6.0, 1H), 5.02 (s, 1H), 6.06 (d, J = 13.0, 1H), 6.83–6.97 (m, 2H), 7.09–7.18 (m with d at 7.11, J = 13.0, 2H), 7.23 (dd, J = 7.8, 1.6, 1H). Resolved signals for the minor isomer: ^{1}H NMR (250 MHz, $CDCl_3$): δ 1.33 (s, 3H), 3.35 (s, 3H), 3.84 (s, 3H), 5.00 (s, 1H), 5.69 (d, J = 7.1, 1H), 6.23 (d, J = 7.1, 1H); HRMS (ESI) of the mixture: calcd for $C_{18}H_{24}O_6Na$ [M^++Na]: 359.1464; found: 359.1460.

Compound **8j**: Colorless oil in 48% yield and as a 92:8 mixture of *E*/*Z* diastereomers. R_f = 0.41 (Hx/EtOAc, 6:1); ^{1}H NMR (250 MHz, $CDCl_3$): δ 1.34 (s, 3H), 1.51 (s, 3H), 3.36 (s, 3H), 3.82 (dd, J = 10.0, 8.2, 1H), 3.89 (dd, J = 10.0, 6.5, 1H), 4.45 (app t, J = 6.8, 1H), 4.63 (d, J = 5.8, 1H), 4.73 (d, J = 5.8, 1H), 5.02 (s, 1H), 5.82 (d, J = 12.9, 1H), 6.98 (d, J = 13.0, 1H), 7.14 (d, J = 8.6, 2H), 7.23 (d, J = 8.6, 2H); ^{13}C NMR (63 MHz, $CDCl_3$): δ 24.9 (CH_3), 26.4 (CH_3), 54.9 (CH_3), 70.3 (CH_2), 81.8 (CH), 84.4 (CH), 85.0 (CH), 105.5 (CH), 109.3 (CH), 112.6 (C), 126.2 (2 × CH), 128.6 (2 × CH), 134.5 (C), 147.8 (CH), 149.3 ppm (C). Resolved signals for the minor isomer: ^{1}H NMR (250 MHz, $CDCl_3$): δ 5.23 (d, J = 7.0, 1H), 6.21 (d, J = 7.0, 1H); ^{13}C NMR (63 MHz, $CDCl_3$): δ 129.2 (2 × CH), 131.2 (2 × CH); HRMS (ESI) of the mixture: calcd for $C_{17}H_{21}O_5ClNa$ [M^++Na]: 365.0940; found: 365.0941.

Compound **8k**: Colorless oil in 45% yield and as a 78:22 mixture of *E*/*Z* diastereomers. R_f = 0.49 (Hx/EtOAc, 6:1); ^{1}H NMR (250 MHz, $CDCl_3$): δ 1.34 (s, 3H), 1.51 (s, 3H), 3.36 (s, 3H), 3.86 (dd, J = 10.0, 7.9, 1H), 3.93 (dd, J = 10.0, 7.1, 1H), 4.47 (app t, J = 7.2, 1H), 4.64 (d, J = 6.1, 1H), 4.74 (d, J = 6.1, 1H), 5.02 (s, 1H), 6.16 (d, J = 13.0, 1H), 6.98 (d, J = 13.0, 1H), 7.10–7.30 (m, 4H); ^{13}C NMR (63 MHz, $CDCl_3$): δ 24.8 (CH_3), 26.3 (CH_3), 54.8 (CH_3), 70.0 (CH_2), 81.7 (CH), 84.3 (CH), 84.9 (CH), 103.0 (CH), 109.2 (CH), 112.5 (C), 125.4 (2 × CH), 126.9 (CH), 129.5 (CH), 129.7 (CH), 132.0 (C), 134.1 (C), 148.9 (CH). Resolved signals for the minor isomer: ^{1}H NMR (250 MHz, $CDCl_3$): δ 1.33 (s, 3H), 1.50 (s, 3H), 3.35 (s, 3H), 4.62 (d, J = 6.2, 1H), 4.71 (d, J = 6.2, 1H), 5.01 (s, 1H), 5.69 (d, J = 7.2, 1H), 6.31 (d, J = 7.2, 1H); ^{13}C NMR (63 MHz, $CDCl_3$): δ 54.7 (CH_3), 85.0 (CH), 101.7 (CH), 109.3 (CH); HRMS (ESI) of the mixture: calcd for $C_{17}H_{21}O_5ClNa$ [M^++Na]: 365.0940; found: 365.0941.

Compound **8l**: Pale yellow oil in 70% yield and as a 81:19 mixture of *E*/*Z* diastereomers. R_f = 0.29 (Hx/EtOAc, 6:1); ^{1}H NMR (250 MHz, $CDCl_3$): δ 1.37 (s, 3H), 1.53 (s, 3H), 3.36 (s, 3H), 3.87–4.02 (m with s at 4.00, 5H, CH_2+CH_3), 4.52 (app t, J = 7.2, 1H), 4.66 (d, J = 6.0, 1H), 4.80 (d, J = 5.9, 1H), 5.05 (s, 1H), 6.44 (d, J = 12.6, 1H), 6.77 (d, J = 8.1, 1H), 6.84 (d, J = 12.6, 1H), 7.31 (d, J = 7.9, 1H), 7.45–7.57 (m, 2H), 8.01 (dd, J = 7.4, 2.0, 1H), 8.29 (dd, J = 7.4, 1.9, 1H); ^{13}C NMR (63 MHz, $CDCl_3$): δ 24.9 (CH_3), 26.4 (CH_3), 54.9 (CH_3), 55.4 (CH_3), 70.3 (CH_2), 81.9 (CH), 84.6 (CH), 85.1 (CH), 103.7 (CH), 103.8 (CH), 109.3 (CH), 112.6 (C), 122.3 (CH), 123.3 (CH), 124.0 (CH), 125.1 (CH), 125.4 (C), 126.1 (C), 126.3 (CH), 132.3 (C), 147.7 (CH), 154.5 (C). Resolved signals for the minor isomer: ^{1}H NMR (250 MHz, $CDCl_3$): δ 1.33 (s, 3H), 1.51 (s, 3H), 3.40 (s, 3H), 4.02 (s, 3H), 4.62 (d, J = 5.9, 1H), 4.74 (d, J = 6.0, 1H), 5.01 (s, 1H), 5.87 (d, J = 7.3, 1H), 6.36 (d, J = 7.3, 1H); ^{13}C NMR (63 MHz, $CDCl_3$): δ 54.9 (CH_3), 84.7 (CH), 103.7 (CH), 109.4 (CH), 112.4 (C), 145.5 (CH); LRMS (ESI): *m*/*z* (%): 405.2 (26), 404.2 (100) [M^++NH_4], 349.2 (15), 297.1 (10), 265.1 (8), 237.1 (8), 215.1 (24), 201.1 (17), 187.1 (9); HRMS (ESI) of the mixture: calcd for $C_{22}H_{26}O_6Na$ [M^++Na]: 409.1620; found: 409.1629.

Compound **8m**: Pale yellow liquid in 81% yield and as a 86:14 mixture of *E*/*Z* diastereomers. R_f = 0.40 (Hx/EtOAc, 4:1); ^{1}H NMR (250 MHz, $CDCl_3$): δ 1.36 (s, 3H), 1.53 (s, 3H), 2.94 (s, 6H), 3.37 (s, 3H), 3.76–3.92 (m, 2H), 4.47 (app t, J = 7.3, 1H), 4.64 (d, J = 6.0, 1H), 4.75 (d, J = 6.0, 1H), 5.03 (s, 1H), 5.85 (d, J = 12.9, 1H), 6.69 (d, J = 8.7, 2H), 6.88 (d, J = 12.9, 1H), 7.14 (d, J = 8.7, 2H); ^{13}C NMR (63 MHz, $CDCl_3$): δ 24.8 (CH_3), 26.2 (CH_3), 40.5 (2 × CH_3), 54.7 (CH_3), 69.8 (CH_2), 81.7 (CH), 84.4 (CH), 84.9 (CH), 106.4 (CH), 109.1 (CH), 112.3 (C), 112.8 (2 × CH), 124.2 (C), 125.8 (2 × CH), 144.7 (CH), 148.9 (CH). Resolved signals for the minor isomer: ^{1}H NMR (250 MHz, $CDCl_3$): δ 2.95 (s, 6H), 5.21 (d, J = 7.0, 1H), 6.07 (d, J = 7.0, 1H), 6.73 (d, J = 8.5, 2H), 7.54 (d, J = 8.8, 2H); ^{13}C NMR (63 MHz, $CDCl_3$): δ 40.4 (2 × CH_3), 81.6 (CH), 84.6 (CH), 85.0 (CH), 109.2 (CH), 112.2 (2 × CH), 129.1 (2 × CH), 143.1 (CH), 148.6 (CH); LRMS (ESI): *m*/*z* (%): 351.2 (21), 350.2 (100) [M^++H], 349.2 (10) [M^+], 282.1 (7); HRMS (ESI) of the mixture: calcd for $C_{19}H_{27}NO_5Na$ [M^++Na]: 372.1779; found: 372.1780.

Compound **8n** *[(E)-major]*: Pale yellow oil in 61% yield. R_f = 0.48 (Hx/EtOAc, 6:1); ^{1}H NMR (250 MHz, $CDCl_3$): δ 1.33 (s, 3H), 1.49 (s, 3H), 3.34 (s, 3H), 3.74–3.87 (m, 2H), 4.43 (app t, J = 7.2, 1H), 4.61 (d, J = 5.9, 1H), 4.70 (d, J = 5.9, 1H), 5.00 (s, 1H), 5.71 (d, J = 12.8, 1H), 6.01 (d, J = 3.2, 1H), 6.32 (dd, J = 3.2, 1.9, 1H), 7.03 (d, J = 12.8, 1H), 7.24 (d, J = 1.5, 1H); ^{13}C NMR (63 MHz, $CDCl_3$): δ 24.8 (CH_3), 26.3 (CH_3), 54.8 (CH_3), 70.2 (CH_2), 81.7 (CH), 84.3 (CH), 84.9 (CH), 96.7 (CH), 104.4 (CH), 109.2 (CH), 110.9 (CH), 112.4 (C), 140.2 (CH), 147.2 (CH), 151.1 (C); HRMS (ESI): calcd for $C_{15}H_{20}O_6Na$ [M^++Na]: 319.1152; found: 319.1150.

Compound **8n** *[(Z)-(minor)]*: Pale yellow oil in 31% yield. R_f = 0.39 (Hx/EtOAc, 6:1); ^{1}H NMR (250 MHz, $CDCl_3$): δ 1.34 (s, 3H), 1.51 (s, 3H), 3.35 (s, 3H), 3.95 (app d, J = 7.4, 2H), 4.47 (app t, J = 7.2, 1H), 4.63 (d, J = 6.0, 1H), 4.75 (d, J = 5.9, 1H), 5.01 (s, 1H), 5.42 (d, J = 6.8, 1H), 6.15 (d, J = 6.8, 1H), 6.41 (dd, J = 3.2, 1.9, 1H), 6.59 (d, J = 3.2, 1H), 7.29 (d, J = 1.6, 1H); ^{13}C NMR (63 MHz, $CDCl_3$): δ 24.9 (CH_3), 26.4 (CH_3), 54.9 (CH_3), 73.8 (CH_2), 81.6 (CH), 84.6 (CH), 85.0 (CH), 97.0 (CH), 108.2 (CH), 109.4 (CH), 111.4 (CH), 112.5 (C), 139.8 (CH), 144.3 (CH), 150.5 (C); HRMS (ESI): calcd for $C_{15}H_{20}O_6Na$ [M^++Na]: 319.1152; found: 319.1141.

Compound **8o**: Colorless oil in 78% yield and as a 71:29 mixture of *E*/*Z* diastereomers. R_f = 0.39 (Hx/EtOAc, 5:1); ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.30 (s, 3H), 1.49 (s, 3H), 3.68 (dd, *J* = 10.8, 5.6, 1H), 3.88–3.93 (m, 1H), 3.95–4.00 (m, 1H), 4.39 (ddd, *J* = 16.6, 9.6, 2.8, 1H), 4.43 (d, *J* = 3.6, 1H), 4.50 (d, *J* = 3.6, 1H), 4.59–4.62 (m with s at 4.60, 3H), 4.79 (d, *J* = 11.2, 1H), 5.91 (d, *J* = 4.0, 1H), 5.99 (d, *J* = 12.8, 1H), 6.81 (d, *J* = 12.8, 1H), 7.15 (d, *J* = 7.2, 2H), 7.22–7.37 (m with s at 7.23, 12H), 7.51 (d, *J* = 7.2, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 26.0 (CH_3), 26.4 (CH_3), 70.5 (CH_2), 72.4 (CH_2), 73.1 (CH_2), 74.8 (CH), 78.1 (CH), 82.0 (CH), 85.2 (CH), 104.8 (CH), 108.3 (CH), 111.8 (C), 124.9 (2 × CH), 125.8 (CH), 127.2 (CH), 127.3 (CH), 127.7 (2 × CH), 128.0 (2 × CH), 128.0 (4 × CH), 128.3 (2 × CH), 135.1 (C), 138.0 (C), 138.1 (C), 145.8 (CH). Resolved signals for the minor isomer: ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.29 (s, 3H), 1.49 (s, 3H), 4.48 (d, *J* = 5.6, 1H), 4.71 (d, *J* = 11.2, 1H), 5.31 (d, *J* = 7.0, 1H), 5.97 (d, *J* = 3.8, 1H), 6.20 (d, *J* = 7.0, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 26.1 (CH_3), 26.4 (CH_3), 70.4 (CH_2), 72.4 (CH_2), 73.1 (CH_2), 75.3 (CH), 78.1 (CH), 82.0 (CH), 82.7 (CH), 104.9 (CH), 107.3 (CH), 111.9 (C), 125.9 (CH), 127.3 (2 × CH), 127.3 (CH), 127.6 (2 × CH), 128.1 (CH), 128.1 (2 × CH), 135.3 (C), 138.1 (C), 138.2 (C), 144.6 (CH); HRMS (ESI) of the mixture: calcd for $C_{31}H_{34}O_6Na$ [M^++Na]: 525.2244; found: 525.2251.

Compound **8p**: Colorless oil in 31% yield and as a single *Z* diastereomer. R_f = 0.58 (Hx/EtOAc, 4:1); ^{1}H NMR (250 MHz, $CDCl_3$): δ 1.12 (s, 9H), 1.32 (s, 3H), 1.48 (s, 3H), 3.68 (dd, *J* = 10.6, 5.7, 1H), 3.89–3.99 (m, 2H), 4.25 (d, *J* = 2.7, 1H), 4.31 (dd, *J* = 9.6, 2.8, 1H), 4.37 (d, *J* = 7.0, 1H), 4.53 (d, *J* = 7.1, 1H), 4.56–4.61 (m with s at 4.61, 3H), 4.80 (d, *J* = 10.9, 1H), 5.78 (d, *J* = 7.0, 1H), 5.90 (d, *J* = 3.6, 1H), 7.27–7.36 (m with s at 7.31, 10H); HRMS (ESI) of the mixture: calcd for $C_{29}H_{38}O_6Na$ [M^++Na]: 505.2556; found: 505.2557.

Compound **8q**: Colorless oil in 58% yield and as a 69:31 mixture of *E*/*Z* diastereomers. R_f = 0.37 (Hx/EtOAc, 6:1); ^{1}H NMR (250 MHz, $CDCl_3$): δ 1.32 (s, 3H), 1.52 (s, 3H), 3.72 (dd, *J* = 10.7, 5.5, 1H), 3.91–4.02 (m, 2H), 4.00–4.52 (m, 3H), 4.61–4.63 (m with s at 4.62, 3H), 4.84 (d, *J* = 11.4, 1H), 5.94 (d, *J* = 3.9, 1H), 5.97 (d, *J* = 12.8, 1H), 6.74 (d, *J* = 12.8, 1H), 6.90–7.11 (m, 4H), 7.25–7.40 (m with s at 7.26, 10H); ^{13}C NMR (63 MHz, $CDCl_3$): δ 26.2 (CH_3), 26.5 (CH_3), 70.5 (CH_2), 72.3 (CH_2), 73.2 (CH_2), 75.0 (CH), 78.1 (CH), 82.1 (CH), 82.3 (CH), 104.9 (CH), 107.3 (CH), 111.9 (C), 115.1 (CH), 115.5 (CH), 126.3 (CH), 126.5 (CH), 127.3 (CH), 127.4 (2 × CH), 127.6 (2 × CH), 128.1 (3 × CH), 128.2 (3 × CH), 131.4 (C), 138.2 (C), 138.3 (C), 145.8 (d, *J* = 1.4, CH), 161.2 (d, *J* = 245.0, C). Resolved signals for the minor isomer: ^{1}H NMR (250 MHz, $CDCl_3$): δ 1.31 (s, 3H), 1.52 (s, 3H), 4.61–4.63 (m with s at 4.61, 3H), 4.75 (d, *J* = 11.2, 1H), 5.29 (d, *J* = 7.0, 1H), 5.99 (d, *J* = 3.8, 1H), 6.19 (d, *J* = 7.0, 1H), 7.50 (dd, *J* = 8.7, 5.5, 2H); ^{13}C NMR (63 MHz, $CDCl_3$): δ 70.3 (CH_2), 75.3 (CH), 82.8 (CH), 85.3 (CH), 105.0 (CH), 106.3 (CH), 112.0 (C), 114.9 (CH), 115.2 (CH), 127.4 (CH), 127.5 (2 × CH), 127.7 (2 × CH), 129.6 (CH), 129.7 (CH), 131.5 (C), 138.1 (C), 138.2 (C), 144.3 (d, *J* = 2.3, CH), 160.9 (d, *J* = 245.9, C); HRMS (ESI) of the mixture: calcd for $C_{31}H_{33}O_6FNa$ [M^++Na]: 543.2150; found: 543.2149.

4.8. General procedure for the preparation of hetero-Diels–Alder products 25–28

In a sealed tube, a mixture of the corresponding enol ether **8** (0.2 mmol) and freshly sublimed and finely ground 2-formyl-1-malondialdehyde[2] **24** (30.0 mg, 0.3 mmol) in a 10:1 mixture of benzene/CH_2Cl_2 (2.0 mL) (previously deoxygenated by 'freeze-vacuum-thaw' treatment) was heated at 70–82 °C for two days. The mixture was diluted with CH_2Cl_2 (7 mL) and the solvents were removed under vacuum. The resulting residue was purified by column chromatography (silica gel, Hx/EtOAc 1:1) or (aluminum oxide, Hx/EtOAc 1:2) to afford the hetero-Diels–Alder products **25–28**, along with the corresponding enol ether **8** (see Scheme 4).

Compound **25a,b**: Colorless oil in 77% yield and as a 2:1 mixture of diastereomers. R_f = 0.22 (Hx/EtOAc, 4:3); ^{1}H NMR (250 MHz, $CDCl_3$): δ 1.27 (s, 3H), 1.33 (s, 3H), 1.41 (s, 3H), 1.47 (s, 3H), 2.59 (br s, 1H, OH), 3.10 (dd, *J* = 9.0, 3.8, 1H), 3.81–3.90 (m, 2H), 3.95 (dd, *J* = 5.8, 4.2, 2H), 4.27 (app quint, *J* = 2.6, 1H), 4.48 (dd, *J* = 7.7, 2.4, 1H), 4.74 (d, *J* = 3.8, 1H), 5.51 (d, *J* = 5.1, 1H), 5.80 (d, *J* = 9.1, 1H), 7.28–7.37 (m with s at 7.32, 6H), 9.36 (s, 1H); ^{13}C NMR (63 MHz, $CDCl_3$): δ 24.2 (CH_3), 24.8 (CH_3), 25.8 (CH_3), 26.0 (CH_3), 48.3 (CH), 61.7 (CH), 66.7 (CH), 68.4 (CH_2), 70.3 (CH), 70.4 (CH), 70.5 (CH), 96.1 (CH), 102.7 (CH), 108.5 (C), 109.2 (C), 121.6 (C), 127.1 (CH), 128.4 (2 × CH), 129.2 (2 × CH), 135.8 (C), 162.9 (CH), 189.4 (CH). Resolved signals for the minor isomer: ^{1}H NMR (250 MHz, $CDCl_3$): δ 3.06 (dd, *J* = 9.3, 3.6, 1H), 4.50 (dd, *J* = 7.9, 2.4, 1H), 4.71 (d, *J* = 3.6, 1H), 5.48 (d, *J* = 5.1, 1H), 5.73 (d, *J* = 9.3, 1H); ^{13}C NMR (63 MHz, $CDCl_3$): δ 24.4 (CH_3), 24.8 (CH_3), 48.4 (CH), 61.8 (CH), 65.6 (CH), 68.7 (CH_2), 70.2 (CH), 70.5 (CH), 70.7 (CH), 102.6 (CH), 108.5 (C), 109.1 (C), 127.2 (CH), 128.2 (2 × CH), 129.1 (2 × CH), 135.9 (C), 162.9 (CH), 189.3 (CH); LRMS (ESI) of the mixture: *m/z* (%): 485 (56) [M^++Na], 480 (23) [M^++NH_4], 446 (17), 445 (70) [M^+−OH], 363 (15), 317 (14), 279 (12), 278 (100); HRMS (ESI) of the mixture: calcd for $C_{24}H_{28}O_8$ [M^+−H_2O]: 444.1776; found: 444.1766.

Compound **26a,b**: Colorless oil in 67% yield and as a 2:1 mixture of diastereomers. R_f = 0.27 (Hx/EtOAc, 1:1); ^{1}H NMR (250 MHz, $CDCl_3$): δ 1.29 (s, 3H), 1.34 (s, 3H), 1.43 (s, 3H), 1.44 (s, 3H), 2.49 (br s, 1H, OH), 3.09 (dd, *J* = 8.7, 3.6, 1H), 3.78–3.96 (m, 4H), 4.29 (app quint. d, *J* = 2.5, 1.0, 1H), 4.52 (d, *J* = 7.7, 1H), 4.72 (d, *J* = 3.8, 1H), 5.53 (d, *J* = 5.1, 1H), 5.76 (d, *J* = 9.0, 1H), 6.98–7.07 (m, 2H), 7.25–7.37 (m, 3H), 9.36 (s, 1H); ^{13}C NMR (63 MHz, $CDCl_3$): δ 24.2 (CH_3), 24.8 (CH_3), 25.8 (CH_3), 25.9 (CH_3), 47.5 (CH), 61.7 (CH), 67.1 (CH), 68.6 (CH_2), 70.2 (CH), 70.4 (CH), 70.7 (CH), 96.1 (CH), 102.7 (CH), 108.5 (C), 109.3 (C), 115.3 (d, *J* = 21.1, 2 × CH), 121.6 (C), 130.9 (d, *J* = 8.3, 2 × CH), 131.4 (d, *J* = 3.2, C), 161.9 (d, *J* = 245.9, C), 162.8 (CH), 189.5 (CH). Resolved signals for the minor isomer: ^{1}H NMR (250 MHz, $CDCl_3$): δ 3.05 (dd, *J* = ?, 3.6, 1H), 4.53 (d, *J* = 7.7, 1H), 4.69 (d, *J* = 3.6, 1H), 5.48 (d, *J* = 4.9, 1H), 5.66 (d, *J* = 9.3, 1H); ^{13}C NMR (63 MHz, $CDCl_3$): δ 24.4 (CH_3), 24.8 (CH_3), 47.6 (CH), 68.7 (CH_2), 70.2 (CH), 70.3 (CH), 102.4 (CH), 108.6 (C), 109.2 (C), 115.1 (d, *J* = 21.1, 2 × CH), 121.6 (C), 130.7 (d, *J* = 8.3, 2 × CH), 162.8 (CH), 189.4 (CH); LRMS (ESI): *m/z* (%): 503 (29) [M^++Na], 463 (6) [M^+−OH], 204 (14), 203 (100); HRMS (ESI) of the mixture: calcd for $C_{24}H_{27}O_8F$ [M^+−H_2O]: 462.1682; found: 462.1673.

Compound **27a,b**: White crystals in 73% yield and as a 1.15:1 mixture of diastereomers. R_f = 0.22 (Hx/EtOAc, 4:3); ^{1}H NMR (250 MHz, $CDCl_3$): δ 1.23 (s, 3H, major), 1.23 (s, 3H, minor), 1.43 (s, 3H, minor), 1.44 (s, 3H, major), 2.42 (br s, 2H, OH), 3.09 (dd, *J* = 9.3, 3.6, 2H), 3.23 (s, 3H, major), 3.25 (s, 3H, minor), 3.59 (app t, *J* = 9.3, 1H), 3.70 (dd, *J* = 9.8, 6.2, 1H), 3.86 (dd, *J* = 9.6, 8.2, 1H), 3.95 (dd, *J* = 9.6, 6.0, 1H), 4.24 (dd, *J* = 7.6, 6.6, 2H), 4.29 (d, *J* = 6.2, 1H), 4.45–4.48 (m with s at 4.46, 3H), 4.74 (d, *J* = 3.3, 1H, major), 4.75 (d, *J* = 4.3, 1H, minor), 4.91 (s, 2H), 5.68 (d, *J* = 9.3, 1H, minor), 5.74 (d, *J* = 9.3, 1H, major), 7.26–7.39 (m with s at 7.38, 12H), 9.38 (s, 2H); ^{13}C NMR (63 MHz, $CDCl_3$): δ 24.6 (CH_3, minor), 24.8 (CH_3, major), 26.2 (CH_3, minor), 26.3 (CH_3, major), 48.1 (CH, major), 48.2 (CH, minor), 54.8 (CH, minor), 54.8 (CH, major), 61.6 (CH, minor), 61.7 (CH, major), 69.8 (CH_2, major), 70.6 (CH_2, minor), 81.5 (CH, minor), 81.7 (CH, major), 84.2 (CH, major), 84.4 (CH, minor), 84.8 (CH, minor), 84.9 (CH, major), 101.7 (CH, major), 102.4 (CH, minor), 109.3 (2 × CH), 112.2 (C, minor), 112.3 (C, major), 121.6 (2 × C), 127.4 (2 × CH), 128.4 (2 × CH, minor), 128.5 (2 × CH, major), 129.1 (2 × CH, major), 129.1 (2 × CH, minor), 135.5 (2 × CH, major), 135.7 (2 × CH, minor), 162.8 (2 × CH), 189.3 (2 × CH); LRMS (ESI): *m/z* (%): 430 (8) [M^++Na+H], 429 (30) [M^++Na], 275 (15), 217 (100), 185 (40); HRMS (ESI) of the mixture: calcd for $C_{21}H_{27}O_8$ [M^++H]: 407.1698; found: 407.1712.

Compound **28a,b**: White solid in 36% yield and as a 8:1 mixture of diastereomers. R_f = 0.20 (Hx/EtOAc, 4:3); mp.: 153–156 °C; ^{1}H NMR (250 MHz, $CDCl_3$): δ 1.33 (s, 6H), 1.42 (s, 3H), 1.50 (s, 3H), 2.43 (br s, 1H, OH), 3.04 (dd, J = 9.2, 3.6, 1H), 3.56 (ddd, J = 8.4, 6.2, 3.8, 1H), 3.75 (dd, J = 8.8, 6.2, 1H), 3.91 (dd, J = 8.8, 3.8, 1H), 4.01 (dd, J = 8.4, 2.8, 1H), 4.30 (d, J = 2.8, 1H), 4.69 (d, J = 3.6, 1H), 4.74 (d, J = 3.6, 1H), 5.79 (d, J = 9.2, 1H), 5.82 (d, J = 3.6, 1H), 7.03 (app t, J = 8.7, 2H), 7.32 (d, J = 8.7, 1H), 7.34 (d, J = 8.7, 1H), 7.39 (s, 1H), 9.41 (s, 1H); ^{13}C NMR (63 MHz, $CDCl_3$): δ 25.1 (CH_3), 26.2 (CH_3), 26.7 (CH_3), 27.0 (CH_3), 48.1 (CH), 61.6 (CH), 66.7 (CH_2), 71.8 (CH), 80.5 (CH), 83.1 (CH), 84.0 (CH), 102.9 (CH), 105.1 (CH), 109.1 (C), 112.0 (C), 115.1 (d, J = 20.9, 2 × CH), 121.8 (C), 131.1 (d, J = 7.8, 2 × CH), 161.8 (d, J = 245.5, C), 162.0 (CH), 189.3 (CH). Resolved signals for the minor isomer: ^{1}H NMR (250 MHz, $CDCl_3$): δ 1.40 (s, 3H), 3.07 (dd, J = 9.3, 3.9, 1H), 9.39 (s, 1H); ^{13}C NMR (63 MHz, $CDCl_3$): δ 26.6 (CH_3), 48.2 (CH); LRMS (ESI): *m/z* (%): 503 (28) [M^++Na], 463 (28) [M^+−OH], 233 (26), 203 (100); HRMS (ESI) of the mixture: calcd for $C_{24}H_{28}O_8F$ [M^+−OH]: 463.1760; found: 463.1761.

4.9. General procedure for the preparation of β-lactams 29–32

To a suspension of pulverized anhydrous sodium carbonate (280 mg, 2.6 mmol) in anhydrous toluene (5 mL), chlorosulfonyl isocyanate (0.17 mL, 2.0 mmol, 280 mg) was added. The mixture was stirred and upon cooling to −70 °C, a solution of enol ether sugar **8** (0.65 mmol) in dry toluene (7.5 mL) was added dropwise. Subsequently, the temperature of the mixture was allowed to rise to −25 °C and maintained for 5 h. The mixture was then cooled to −70 °C, diluted with toluene (17 mL), treated with sodium bis(2-methoxyethoxy)aluminum hydride (Red-Al) (0.82 mL, 2.6 mmol, 65 wt % solution in toluene), and left for 45 min whereas the temperature was maintained (−70 °C). Subsequently, the temperature was allowed to rise to 0 °C, water (2 mL) was added, and the mixture was intensively stirred for 15 min. The suspension was filtered through Celite, the solvent was evaporated and the residue was purified by flash column chromatography (Hx/EtOAc 2:1, then Hx/EtOAc 1:1) to give β-lactams **29–32**.

Compound **29**: Pale yellow oil in 77% yield and as a 1.3:1 mixture of diastereomers. R_f = 0.28 (Hx/EtOAc, 3:2); ^{1}H NMR (250 MHz, $CDCl_3$): δ 1.35 (s, 6H), 1.45 (s, 3H), 1.55 (s, 3H), 3.75 (dd, J = 10.9, 5.2, 1H), 3.84–4.00 (m, 2H), 4.25 (dd, J = 7.9, 1.7, 1H), 4.28 (br s, 1H), 4.36 (dd, J = 4.8, 2.5, 1H), 4.64 (dd, J = 7.9, 2.5, 1H), 5.05 (d, J = 1.1, 1H), 5.57 (d, J = 4.8, 1H), 6.82 (br s, 1H), 7.29–7.38 (m, 5H); ^{13}C NMR (63 MHz, $CDCl_3$): δ 24.2 (CH_3), 24.8 (CH_3), 25.8 (CH_3), 25.9 (CH_3), 62.3 (CH), 66.1 (CH), 68.0 (CH_2), 70.4 (CH), 70.6 (CH), 70.8 (CH), 85.7 (CH), 96.2 (CH), 108.7 (C), 109.5 (C), 127.5 (2 × CH), 128.2 (CH), 128.8 (2 × CH), 133.4 (C), 167.2 (C). Resolved signals for the minor isomer: ^{1}H NMR (250 MHz, $CDCl_3$): δ 1.47 (s, 3H), 4.59 (dd, J = 7.3, 2.7, 1H), 4.97 (d, J = 1.4, 1H); ^{13}C NMR (63 MHz, $CDCl_3$): δ 24.4 (CH_3), 24.7 (CH_3), 25.8 (CH_3), 25.9 (CH_3), 63.1 (CH), 67.4 (CH_2), 70.2 (CH), 70.7 (CH), 87.2 (CH), 96.4 (CH), 108.6 (C), 109.4 (C); LRMS (ESI) of the mixture: *m/z* (%): 428.2 (20) [M^++Na], 406.2 (33) [M^++H], 179.1 (32), 145.2 (100); HRMS (ESI) of the mixture: calcd for $C_{21}H_{28}NO_7$ [M^++H]: 406.1857; found: 406.1861.

Compound **30**: Colorless oil in 72% yield and as a 1.2:1 mixture of diastereomers. R_f = 0.20 (Hx/EtOAc, 2:1); R_f = 0.46 (Hx/EtOAc, 1:1); ^{1}H NMR (250 MHz, $CDCl_3$): δ 1.35 (s, 3H), 1.50 (s, 3H), 3.34 (s, 3H), 3.57 (dd, J = 10.1, 7.9, 1H), 3.66 (dd, J = 10.1, 6.2, 1H), 4.25 (br s, 1H), 4.34 (app q, J = 7.4, 1H), 4.59 (dd, J = 6.0, 2.4, 1H), 4.64 (d, J = 6.3, 1H), 4.71 (d, J = 6.3, 1H), 4.98 (br s, 1H), 5.00 (s, 1H), 6.65 (br s, 1H, NH), 7.29–7.40 (m, 5H); ^{13}C NMR (63 MHz, $CDCl_3$): δ 24.9 (CH_3), 26.4 (CH_3), 55.3 (CH_3), 63.3 (CH), 69.1 (CH_2), 81.5 (CH), 84.7 (CH), 84.9 (CH), 86.1 (CH), 109.5 (CH), 112.8 (C), 127.5 (2 × CH), 127.8 (CH), 128.9 (2 × CH), 133.1 (C), 167.0 (C). ^{1}H NMR (250 MHz, C_6D_6): δ 1.18 (s, 3H), 1.49 (s, 3H), 2.98 (s, 3H), 3.12–3.24 (m, 2H), 4.09 (br s, 1H), 4.36–4.48 (m, 3H), 4.58 (s, 1H), 5.03 (s, 1H), 6.73 (br s, 1H, NH), 7.03–7.19 (m, 5H). Resolved signals for the minor isomer: ^{1}H NMR (250 MHz, $CDCl_3$): δ 1.33 (s, 3H); ^{13}C NMR (63 MHz, $CDCl_3$): δ 55.2 (CH_3), 63.1 (CH), 70.0 (CH_2), 84.9 (CH), 85.4 (CH), 86.0 (CH), 109.5 (CH), 112.7 (C), 166.9 (C); ^{1}H NMR (250 MHz, C_6D_6): δ 1.17 (s, 3H), 1.48 (s, 3H), 2.99 (s, 3H), 4.12 (br s, 1H), 4.36–4.48 (m, 2H), 4.53 (d, J = 5.8, 1H), 4.58 (s, 1H), 5.01 (s, 1H), 5.81 (br s, 1H, NH), 7.03–7.19 (m, 5H); LRMS (ESI) of the mixture: *m/z* (%): 367.1 (23) [M^++NH_4], 350.1 (100) [M^++H], 319.2 (30), 219.1 (33); HRMS (ESI) of the mixture: calcd for $C_{18}H_{24}NO_6$ [M^++H]: 350.1596; found: 350.1606.

Compound **31**: Colorless oil in 67% yield and as a single diastereomer. R_f = 0.17 (Hx/EtOAc, 3:2); IR (CH_2Cl_2): $[\nu]_{max}$ (cm^{-1}) = 3512 (br), 3265 (br), 1960, 1770, 1499, 1458, 1382, 1107, 1032, 743, 709; ^{1}H NMR (250 MHz, $CDCl_3$): δ 1.29 (s, 3H), 1.46 (s, 3H), 3.34 (dd, J = 8.7, 5.0, 1H), 3.52 (dd, J = 10.9, 5.1, 1H), 3.70 (dd, J = 10.8, 1.7, 1H), 3.98 (d, J = 11.8, 1H), 4.13 (d, J = 3.2, 1H), 4.21–4.31 (m, 1H), 4.37 (dd, J = 4.3, 2.0, 1H), 4.44 (d, J = 3.6, 1H), 4.49 (s, 2H), 4.55 (d, J = 11.7, 1H), 5.19 (dd, J = 4.4, 1H), 5.79 (d, J = 3.7, 1H), 6.81 (br s, 1H), 7.18–7.39 (m with s at 7.31, 15H); ^{13}C NMR (63 MHz, $CDCl_3$): δ 26.3 (CH_3), 26.7 (CH_3), 62.1 (CH), 70.0 (CH_2), 71.6 (CH_2), 73.1 (CH_2), 75.4 (CH), 78.5 (CH), 82.1 (CH), 82.2 (CH), 82.7 (CH), 104.9 (CH), 112.0 (C), 127.2 (2 × CH), 127.4 (CH), 127.4 (2 × CH), 127.6 (CH), 127.9 (CH), 128.2 (4 × CH), 128.4 (2 × CH), 129.7 (2 × CH), 130.9 (C), 138.3 (C), 138.6 (C), 168.2 (C). LRMS (ESI) of the mixture: *m/z* (%): 568.1 (25) [M^++Na], 546.2 (26) [M^++H], 421.2 (20), 392.0 (16), 391.2 (42), 375.0 (26), 370.2 (20), 318.9 (29), 264.1 (21), 246.0 (19), 241.9 (35), 221.0 (88), 216.1 (67), 215.0 (100); HRMS (ESI): calcd for $C_{32}H_{36}NO_7$ [M^++H]: 546.2481; found: 546.2487.

Compound **32**: Colorless oil in 65% yield and as a single diastereomer. R_f = 0.22 (Hx/EtOAc, 3:2); ^{1}H NMR (250 MHz, $CDCl_3$): δ 1.31 (s, 3H), 1.49 (s, 3H), 3.72 (dd, J = 10.4, 5.0, 1H), 3.90–3.99 (m with s at 3.95, 2H), 4.11 (d, J = 3.0, 1H), 4.17 (s, 1H), 4.22 (d, J = 11.4, 1H), 4.36 (dd, J = 9.5, 2.8, 1H), 4.57 (d, J = 3.8, 1H), 4.60 (s, 2H), 4.84 (d, J = 11.4, 1H), 4.97 (d, J = 1.1, 1H), 5.93 (d, J = 3.7, 1H), 6.90 (br s, 1H), 6.94–7.10 (m, 6H), 7.23–7.38 (m, 8H); ^{13}C NMR (63 MHz, $CDCl_3$): δ 26.2 (CH_3), 26.6 (CH_3), 62.9 (CH), 70.2 (CH_2), 71.8 (CH_2), 73.4 (CH_2), 75.6 (CH), 78.2 (CH), 80.8 (CH), 82.7 (CH), 85.5 (CH), 105.0 (CH), 112.1 (C), 115.8 (d, J = 21.6, 2 × CH), 127.0 (2 × CH), 127.5 (CH), 127.5 (CH), 127.6 (2 × CH), 128.3 (4 × CH), 128.6 (d, J = 3.2, C), 129.1 (d, J = 8.3, 2 × CH), 138.0 (C), 138.1 (C), 166.8 (C), the quaternary carbon C–F was not resolved; LRMS (ESI): *m/z* (%): 564.2 (7) [M^++H], 414.3 (5), 359.1 (10), 338.2 (15), 293.0 (32), 280.1 (18), 279.1 (100), 263.1 (62); HRMS (ESI): calcd for $C_{32}H_{35}FNO_7$ [M^++H]: 564.2387; found: 564.2406.

4.10. General procedure for the preparation of *N*-methylthio β-lactams 33–36

To a solution of the corresponding β-lactam **29–32** (0.25 mmol) in THF (10 mL) at −78 °C was added *n*-BuLi (0.69 mL, 1.11 mmol, 1.6 M in hexanes); 4.5 equiv due to the presence of ca. 3 equiv of H_2O with the β-lactam **29–32**. After 1 h, methyl methanethiosulfonate (0.11 mL, 1.11 mmol, 140 mg) was added at −78 °C and the reaction mixture was stirred for 7 h while warming to room temperature. The mixture is poured into aqueous NH_4Cl (20 mL) and extracted with ethyl acetate (3 × 30 mL). The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was purified by flash chromatography using Hx/EtOAc 4:1 and CH_2Cl_2/Hx 7:1 for compounds **33** and **34**, and by flash column chromatography (Hx/EtOAc 4:1) for compounds **35** and **36**.

Compound **33**: Colorless oil in 62% yield and as a 1.3:1 mixture of diastereomers. R_f = 0.28 (Hx/EtOAc, 4:1); ^{1}H NMR (250 MHz,

$CDCl_3$): δ 1.35 (s, 6H), 1.45 (s, 3H), 1.53 (s, 3H), 2.58 (s, 3H), 3.87 (dd, J = 9.5, 6.2, 1H), 4.00–4.22 (m, 2H), 4.29 (dd, J = 7.9, 1.6, 1H), 4.34 (dd, J = 5.0, 2.5, 1H), 4.37 (br s, 1H), 4.64 (dd, J = 7.9, 2.5, 1H), 5.08 (d, J = 1.4, 1H), 5.52 (d, J = 5.2, 1H), 7.28 (d, J = 7.6, 2H), 7.34 (t, J = 7.5, 3H); ^{13}C NMR (63 MHz, $CDCl_3$): δ 23.0 (CH_3), 24.4 (CH_3), 24.9 (CH_3), 25.9 (CH_3), 26.0 (CH_3), 63.0 (CH), 66.8 (CH), 68.4 (CH_2), 70.4 (CH), 70.6 (CH), 70.9 (CH), 93.2 (CH), 96.2 (CH), 108.6 (C), 109.4 (C), 127.3 (2 × CH), 127.7 (CH), 128.8 (2 × CH), 133.0 (C), 165.6 (C). Resolved signals for the minor isomer: ^{1}H NMR (250 MHz, $CDCl_3$): δ 2.54 (s, 3H), 4.54 (dd, J = 7.7, 2.4, 1H), 5.54 (d, J = 5.2, 1H), 7.55 (app td, J = 7.9, 1.6, 5H); LRMS (ESI) of the mixture: m/z (%): 474.2 (16) [M^++Na], 452.0 (100) [M^++H], 394.2 (14), 325.2 (15), 303.1 (25); HRMS (ESI) of the mixture: calcd for $C_{22}H_{29}NO_7SNa$ [M^++Na]: 474.1554; found: 474.1563.

Compound **34**: Colorless oil in 57% yield and as a 1.2:1 mixture of diastereomers. R_f = 0.30 (Hx/EtOAc, 4:1); ^{1}H NMR (250 MHz, $CDCl_3$): δ 1.34 (s, 3H, major.), 1.35 (s, 3H, minor.), 1.51 (s, 6H), 2.59 (s, 3H, major.), 2.59 (s, 3H, minor.), 3.30 (s, 3H, minor.), 3.32 (s, 3H, major.), 3.65–3.67 (m, 2H), 3.87–4.00 (m, 2H), 4.32 (d, J = 1.6, 1H, minor.), 4.33 (d, J = 1.6, 1H, major.), 4.38 (app q, J = 7.2, 2H), 4.60 (d, J = 5.9, 1H, minor.), 4.62 (d, J = 5.9, 1H, major.), 4.69 (d, J = 5.9, 1H, major.), 4.75 (d, J = 5.9, 1H, minor.), 4.98 (d, J = 1.6, 2H), 4.99 (s, 1H, major.), 5.00 (s, 1H, minor.), 7.22 (d, J = 7.6, 4H), 7.34 (t, J = 7.5, 6H); ^{13}C NMR (63 MHz, $CDCl_3$): δ 23.2 (CH_3, minor.), 23.2 (CH_3, major.), 24.9 (2 × CH_3), 26.4 (2 × CH_3), 55.0 (2 × CH_3), 63.7 (CH, major.), 63.9 (CH, minor.), 70.4 (CH_2, major.), 70.5 (CH_2, minor.), 81.7 (2 × CH), 84.8 (CH, major.), 84.9 (CH, minor.), 85.0 (CH, major.), 85.0 (CH, minor.), 86.0 (CH, major.), 86.1 (CH, minor.), 109.3 (CH, major.), 109.4 (CH, minor.), 112.6 (2 × C), 127.2 (4 × CH), 128.0 (2 × CH), 129.0 (4 × CH), 132.8 (C, major.), 132.8 (C, minor.), 166.0 (2 × C). LRMS (ESI) of the mixture: m/z (%): 418.2 (18) [M^++Na], 396.2 (38) [M^++H], 364.1 (77), 279.2 (29), 246.0 (36), 224.0 (58), 194.2 (100); HRMS (ESI) of the mixture: calcd for $C_{19}H_{25}NO_6SNa$ [M^++Na]: 418.1293; found: 418.1301.

Compound **35**: Colorless oil in 65% yield and as a single diastereomer. R_f = 0.28 (Hx/EtOAc, 4:1); $[\alpha]_D^{18} = -7.6$ (c 0.5, CH_2Cl_2); ^{1}H NMR (250 MHz, $CDCl_3$): δ 1.41 (s, 6H), 1.57 (s, 3H), 2.58 (s, 3H), 3.76 (dd, J = 10.6, 4.9, 1H), 3.92–4.02 (m, 2H), 4.15 (d, J = 11.5, 1H), 4.29 (br s, 1H), 4.40–4.44 (m with s at 4.44, 2H), 4.64 (s, 2H), 4.82 (d, J = 9.0, 1H), 4.85 (s, 1H), 5.10 (d, J = 1.3, 1H), 6.03 (d, J = 3.7, 1H), 7.03–7.13 (m, 4H), 7.28–7.41 (m, 11H); ^{13}C NMR (63 MHz, $CDCl_3$): δ 22.8 (CH_3), 26.3 (CH_3), 26.6 (CH_3), 64.6 (CH), 70.2 (CH_2), 71.4 (CH_2), 73.3 (CH_2), 75.5 (CH), 78.2 (CH), 81.9 (CH), 83.2 (CH), 92.1 (CH), 104.9 (CH), 112.1 (C), 126.9 (2 × CH), 127.2 (2 × CH), 127.3 (CH), 127.5 (CH), 127.5 (2 × CH), 128.0 (CH), 128.2 (2 × CH), 128.3 (2 × CH), 129.0 (2 × CH), 132.5 (C), 138.1 (C), 138.2 (C), 169.5 (C); LRMS (ESI): m/z (%): 614.1 (6) [M^++Na], 609.2 (43) [M^++NH_4], 592.2 (11) [M^++H], 535.2 (5), 418.1 (25), 279.0 (19), 277.0 (100); HRMS (ESI): calcd for $C_{33}H_{37}NO_7SNa$ [M^++Na]: 614.2178; found: 614.2168.

Compound **36**: Colorless oil in 68% yield and as a single diastereomer. R_f = 0.25 (Hx/EtOAc, 4:1); ^{1}H NMR (250 MHz, $CDCl_3$): δ 1.39 (s, 6H), 1.55 (s, 3H), 2.57 (s, 3H), 3.74 (dd, J = 10.6, 4.9, 1H), 3.92 (dd, J = 9.9, 4.9, 1H), 3.99 (dd, J = 10.6, 1.4, 1H), 4.16 (d, J = 11.7, 1H), 4.21 (d, J = 1.3, 1H), 4.39–4.44 (m with s at 4.40, 2H), 4.62 (s, 2H), 4.82 (d, J = 3.8, 1H), 4.85 (d, J = 11.7, 1H), 5.04 (d, J = 1.3, 1H), 6.01 (d, J = 3.6, 1H), 6.93 (app d, J = 7.1, 4H), 7.12 (d, J = 5.5, 1H), 7.13 (d, J = 7.3, 1H), 7.27–7.39 (m with s at 7.37, 8H); ^{13}C NMR (63 MHz, $CDCl_3$): δ 22.9 (CH_3), 26.3 (CH_3), 26.6 (CH_3), 63.8 (CH), 70.1 (CH_2), 71.3 (CH_2), 73.4 (CH_2), 75.6 (CH), 78.1 (CH), 81.9 (CH), 83.2 (CH), 92.1 (CH), 104.9 (CH), 112.2 (C), 115.9 (d, J = 21.6, 2 × CH), 126.6 (2 × CH), 127.5 (3 × CH), 128.2 (2 × CH), 128.3 (2 × CH), 128.9 (d, J = 8.3, 2 × CH), 138.1 (C), 138.1 (C), 160.9 (d, J = 249.1, C), 169.3 (C); HRMS (ESI): calcd for $C_{33}H_{37}NO_7FS$ [M^++H]: 578.2543; found: 578.2552.

4.11. Testing of antimicrobial susceptibilities (Kirby–Bauer well diffusion)

S. aureus (ATCC 25923) and MRSA (ATCC 43300, ATCC 33591) were purchased from American Type Culture Collection sources. *Culture preparation*: from a freezer stock in tryptic soy broth (Difco Laboratories, Detroit, MI) and 20% glycerol, a culture of each microorganism was transferred with a sterile Dacron swab to Trypticase® Soy Agar (TSA) plates (Becton–Dickinson Laboratories, Cockeysville, MD), streaked for isolation, and incubated at 37 °C for 24 h. A 10^8 standardized cell count suspension was then made in sterile phosphate-buffered saline (pH 7.2) and swabbed across fresh TSA plates. Prior to swabbing with the culture solution, 20 μL of a 1 mg/mL stock solution of the test compound in dimethylsulfoxide (DMSO) was added to a 6-mm diameter well bored into the agar. The plates were swabbed uniformly with the test microbe compound mentioned above and then incubated for 24 h at 37 °C. The antimicrobial susceptibilities were determined by measuring the diameter of the growth inhibition zone appearing around each well.

4.12. Determination of minimum inhibitory concentrations

The minimum inhibitory concentration (MIC) values of the lactams were determined for *S. aureus* and MRSA by serial dilution in agar, according to NCCLS protocols.[32] The test medium was prepared in 24-well plates (Costar 3524, Cambridge, MA) by adding the test drug in DMSO to Mueller–Hinton II agar (Becton–Dickinson Laboratories, Cockeysville, MD) to bring the total volume in each well to 1.0 mL. Starting with an initial well concentration of 256 μg of drug/mL, each sequential dilution contained half the concentration of the drug. The medium was allowed to solidify at room temperature for 24 h before inoculation with the bacteria. Using a sterilized inoculating loop, a small amount of each standardized *Staphylococcus* strain cultured on TSA plates for 24 h was transferred into sterile test tubes containing 5 mL of TSA broth and was incubated at 37 °C for 24 h. One microliter of each culture was then applied to the appropriate well of Mueller–Hinton agar and was incubated at 37 °C overnight. After 24 h, the MICs were determined as the lowest concentration of the drug where bacterial growth was visibly inhibited.

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References

1. For general reviews, see: (a) Boutagy, J.; Thomas, R. *Chem. Rev.* **1974**, *74*, 87–89; (b) Maryanoff, B. E.; Reitz, A. B. *Chem. Rev.* **1989**, *89*, 863–927; (c) Kelly, S. E.. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon: Oxford, 1991; Vol. 1, p 729; (d) Vedejs, E.; Peterson, M. J. *Top. Stereochem.* **1994**, *21*, 1–157; (e) Petasis, N. A.; Hu, Y. H. *Curr. Org. Chem.* **1997**, *1*, 249–286; (f) Shen, Y. C. *Acc. Chem. Res.* **1998**, *31*, 584–592; (g) van Staden, L. F.; Gravestock, D.; Ager, D. J. *Chem. Soc. Rev.* **2002**, *31*, 195–200.
2. (a) Julia, M.; Paris, J.-M. *Tetrahedron Lett.* **1973**, 4833–4836; (b) Kocienski, P. J.; Lythgoe, B.; Waterhouse, I. *J. Chem. Soc., Perkin Trans. 1* **1980**, 1045.
3. For a selection of examples, see: (a) Prilezhaeva, E. N. *Russ. Chem. Rev.* **2000**, *69*, 367–408; (b) Matthieu Corbet, M.; Bourdon, B.; Gueyrard, D.; Goekjia, P. G. *Tetrahedron Lett.* **2008**, *49*, 750–754; (c) Alonso, D. A.; Nájera, C.; Varea, M. *Tetrahedron Lett.* **2004**, *45*, 573–577; (d) Pospíšil, D. J.; Markó, I. E. *Tetrahedron Lett.* **2006**, *47*, 5933–5937; (e) Allen, J. V.; Green, A. P.; Hardy, S.; Heron, N. M.; Lee, A. T. L.; Thomas, E. J. *Tetrahedron Lett.* **2008**, *49*, 6352–6355.
4. (a) Baudin, J. B.; Hareau, G.; Julia, S. A.; Ruel, O. *Tetrahedron Lett.* **1991**, *32*, 1175–1178; (b) Baudin, J. B.; Hareau, G.; Julia, S. A.; Lome, R.; Ruel, O. *Bull. Soc. Chim. Fr.* **1993**, *130*, 856–878; (c) Baudin, J. B.; Hareau, G.; Julia, S. A.; Ruel, O. *Bull. Soc. Chim. Fr.* **1993**, *130*, 336–357; (d) Blakemore, P. R.; Cole, W. J.;

Kocienski, P. J.; Morley, A. *Synlett* **1998**, 26–28; (e) Kocienski, P. J.; Bell, A.; Blakemore, P. R. *Synlett* **2000**, 365–366; (f) Blakemore, P. R. *J. Chem. Soc., Perkin Trans. 1* **2002**, 2563–2585; (g) Charette, A. B.; Berthelette, C.; St-Martin, D. *Tetrahedron Lett.* **2001**, *42*, 6619; (h) Charette, A. B.; Berthelette, C.; St-Martin, D. *Tetrahedron Lett.* **2001**, *42*, 5149–5153; (i) Compostella, F.; Franchini, L.; Panza, L.; Prosperi, D.; Ronchetti, F. *Tetrahedron* **2002**, *58*, 4425–4428.

5. For lead references on Julia couplings relating to carbohydrates, see: (a) Bourdon, B.; Corbet, M.; Fontaine, P.; Goekjian, P. G.; Gueyrard, D. *Tetrahedron Lett.* **2008**, *49*, 747–749; (b) Corbet, M.; Bourdon, B.; Gueyrard, D.; Goekjian, P. G. *Tetrahedron Lett.* **2008**, *49*, 750–754; (c) Chandrasekhar, S.; Jagadeshwar, V.; Prakash, S. J. *Tetrahedron Lett.* **2005**, *46*, 3127–3129; (d) Yadav, J. S.; Reddy, P. V.; Chandraiah, L. *Tetrahedron Lett.* **2007**, *48*, 145–148.
6. Surprenant, S.; Chan, W. Y.; Berthelette, C. *Org. Lett.* **2003**, *5*, 4851–4854.
7. (a) Tulshian, D. B.; Fraser-Reid, B. *J. Org. Chem.* **1984**, *49*, 518–522; (b) Tulshian, D. B.; Tsang, R.; Fraser-Reid, B. *J. Org. Chem.* **1984**, *49*, 2347–2355.
8. Vidal, T.; Haudrechy, A.; Langlois, Y. *Tetrahedron Lett.* **1999**, *40*, 5677–5680.
9. (a) Godage, H. Y.; Fairbanks, A. J. *Tetrahedron Lett.* **2000**, *41*, 7589–7593; (b) Chayajarus, K.; Chambers, D. J.; Chughtai, M. J.; Fairbanks, A. J. *Org. Lett.* **2004**, *6*, 3797–3800.
10. Dettinger, H. M.; Lehmann, J.; Wallenfels, K. *Carbohydr. Res.* **1980**, *87*, 63–70.
11. Vankar, Y. D.; Vankar, P. S.; Behrendt, M.; Schmidt, R. R. *Tetrahedron* **1991**, *47*, 9985–9992.
12. Marra, A.; Esnault, J.; Veyrieres, A.; Sinay, P. *J. Am. Chem. Soc.* **1992**, *114*, 6354–6360.
13. (a) Chenault, H. K.; Castro, A. *Tetrahedron Lett.* **1994**, *35*, 9145–9148; (b) Chenault, H. K.; Castro, A.; Chafin, L. F.; Yang, J. *J. Org. Chem.* **1996**, *61*, 5024–5031.
14. (a) Boons, G.-J.; Isles, S. *Tetrahedron Lett.* **1994**, *35*, 3593–3596; (b) Boons, G.-J.; Isles, S. *J. Org. Chem.* **1996**, *61*, 4262–4271; (c) Bai, Y.; Boons, G.-J.; Burton, A.; Johnson, M.; Haller, M. *J. Carbohydr. Chem.* **2000**, *19*, 939–958.
15. (a) Handerson, S.; Schlaf, M. *Org. Lett.* **2002**, *4*, 407–409; (b) Bosch, M.; Handerson, S.; Schlaf, M. *J. Carbohydr. Chem.* **2008**, *27*, 103–112.
16. Labeau, M.-P.; Cramail, H.; Deffieux, A. *Macromol. Chem. Phys.* **1998**, *199*, 335–342.
17. Yuan, J.; Lindner, K.; Frauenrath, H. *J. Org. Chem.* **2006**, *71*, 5457–5467.
18. Hughes, K. D.; Nguyen, T.-L. M.; Dyckman, D.; Dulay, D.; Boyko, W. J.; Giuliano, R. M. *Tetrahedron: Asymmetry* **2005**, *16*, 273–282.
19. All reagents and solvents were previously deoxygenated by 'freeze-vacuum-thaw' treatment.
20. Tietze, L.-F.; Glusenkamp, K.-H.; Harmn, K.; Remberg, G.; Gottiengen, G. M. *Tetrahedron Lett.* **1982**, *23*, 1147–1150.
21. ^{1}H, ^{13}C, DEPT, gHSQC, gHMBC, gCOSY, and NOESY NMR spectra were measured.
22. 'β-Lactams', Cristina Coates, Jasmine Kabir, Edward Turos, Compounds with Four and Three Carbon-Heteroatom Bonds, Science of Synthesis, Houben-Weyl Methods of Molecular Transformations, 2005; Vol. 21, pp 609–646.
23. For studies on N-thiolated β-lactam antibiotics, see: (a) Revell, K. D.; Heldreth, B.; Long, T. E.; Jang, S.; Turos, E. *Bioorg. Med. Chem.* **2007**, *15*, 2453–2467; (b) Turos, E.; Coates, C.; Shim, J.-Y.; Wang, Y.; Leslie, M.; Long, T. E.; Reddy, G. S. K.; Ortiz, A.; Culbreath, M.; Dickey, S.; Lim, D. V.; Alonso, E.; Gonzalez, J. *Bioorg. Med. Chem.* **2005**, *13*, 6289–6308; (c) Turos, E.; Long, T. E.; Konaklieva, M. I.; Coates, C.; Shim, J.-Y.; Dickey, S.; Lim, D. V.; Cannons, A. *Bioorg. Med. Chem. Lett.* **2002**, *12*, 2229–2231.
24. (a) Chmielewski, M.; Kałuza, Z. *J. Org. Chem.* **1986**, *51*, 2397–2398; (b) Kałuza, Z.; Abramski, W.; Bełzecki, Z.; Grodner, J.; Mostowicz, D.; Urbanski, R.; Chmielewski, M. *Synlett* **1994**, 539–541; (c) Kałuza, Z.; Furman, B.; Chmielewski, M. *Tetrahedron: Asymmetry* **1995**, *6*, 1719–1730; (d) Chmielewski, M.; Kałuza, Z.; Furman, B. *Chem. Commun.* **1996**, 2689–2696; (e) Lysek, R.; Furman, B.; Kałuza, Z.; Frelek, J.; Suwinska, K.; Urbanczyk-Lipkowska, Z.; Chmielewski, M. *Tetrahedron: Asymmetry* **2000**, *11*, 3131–3150.
25. Jarrahpour, A. A.; Shekarriz, M.; Taslimi, A. *Molecules* **2004**, *9*, 29–38.
26. This base is used to neutralize acidic contaminations (SO_3, HCl) present in the commercially available CSI reagent.
27. The analogous [2+2]-cycloaddition reaction carried out with enol ether **8a** furnished the corresponding enol ether C5,C6-acetonide deprotected diol, which is formed after a β-hydrogen elimination induced by Red-Al.
28. Perrin, D. D.; Armarego, W. L. F. *Purification of Laboratory Chemicals*; Pergamon: Oxford, 1988.
29. Budesínský, M.; Fiedler, P.; Arnold, Z. *Synthesis* **1989**, 858–860.
30. Mahender, G.; Ramu, R.; Ramesh, C.; Das, B. *Chem. Lett.* **2003**, *32*, 734–735.
31. For the preparation of $NaHSO{\cdot}SiO_2$ catalyst, see: Breton, G. W. *J. Org. Chem.* **1997**, *62*, 8952–8954.
32. NCCLS (National Committee for Clinical Laboratory Standards) Methods for Dilution of Antimicrobial Susceptibility Tests for Bacteria that Grow Aerobically. NCCLS Document M7-A4, 1997; Vol. 17, No. 2.