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Stereocontrolled 1,3-dipolar cycloadditions using Oppolzer's camphor sultam as the chiral auxiliary for carbonyl stabilized azomethine ylides

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Abstract—Two complementary approaches to substituted pyrrolidines via stereocontrolled 1,3-dipolar cycloaddition reactions of chiral azomethine ylides are described. In one approach, chiral azomethine ylides were generated by thermolysis of aziridine carboxylate sultams and trapped with a variety of dipolarophiles to give good yields of the corresponding cycloadducts. In the second approach, chiral azomethine ylides were generated from glycyl sultams by 'imine tautomerization' and trapped with dipolarophiles to give good yields of the corresponding cycloadducts.

1. Introduction

Asymmetric 1,3-dipolar cycloaddition reactions of azomethine ylides[1] (Fig. 1) offer an effective means to access pyrrolidine substructures **1** found in many biologically active compounds.[2] Stereocontrol in these reactions can be achieved through the use of chiral auxiliaries that are attached either to the dipoles **2** or dipolarophiles **3**. While good stereocontrol has been reported for bimolecular cycloadditons using both strategies, the development of a suitable chiral auxiliary for azomethine ylides has received less attention.[3] In this context, there are five issues which need to be considered when evaluating the utility of chiral auxiliaries for asymmetric cycloadditions. These are (1) availability of the auxiliary, (2) diastereofacial selectivity, (3) *endo*/*exo* selectivity, (4) geometry of 1,3-disubstituted ylides, and (5) auxiliary removal/recovery. Suffice it to say that none of the chiral systems for azomethine ylides reported so far appears to satisfy all of these requirements. Particularly noteworthy is the fact that all of the covalently attached azomethine ylide auxiliaries require destructive removal. It was in this context that we initiated studies whose goal was to develop a recoverable chiral auxiliary for azomethine ylides. This work has resulted in stereocontrolled syntheses of a variety of pyrrolidine systems using azomethine ylides which incorporate Oppolzer's camphor sultam as a recoverable chiral auxiliary.[4] We now report the full details of our work in the context of *bimolecular* azomethine ylide cycloadditions.[5]

2. Results and discussion

Our analysis of this problem led us to consider the use of chiral auxiliaries which would exert diastereofacial bias under purely thermal conditions—that is without the need of Lewis acids. Analysis of the transition state models put forth by Kim and Curran[6] for thermal Diels–Alder and nitrile oxide cycloadditions to C(sp^2)–COX* dienophiles and dipolarophophiles (where X*=Oppolzer's camphor sultam) suggested to us that azomethine ylides which incorporate this substructure might also benefit from the same diastereofacial control elements. Thus, of the 4 possible combinations of C(α)–CO and CO–N orientations, the (*s-cis*, *anti*) conformer should be preferred on stereoelectronic grounds (Fig. 2). When the auxiliary is ultimately derived from (−)-camphor (as in this paper), reagents should approach the prochiral α-carbon preferentially from its si-face (opposite the pro-S sulfonimide oxygen). This argument presumes that potentially competing cycloadditions through the other 3 conformers will not proceed at significantly faster rates relative to (*s-cis*, *anti*)

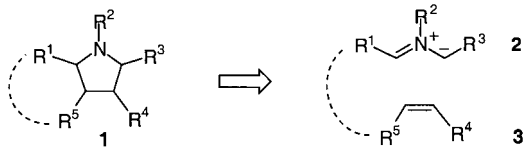

Figure 1. General approach to pyrrolidines via 1,3-dipolar cycloaddition.

Keywords: cycloadditions; pyrrolidines; stereocontrol; sultams.

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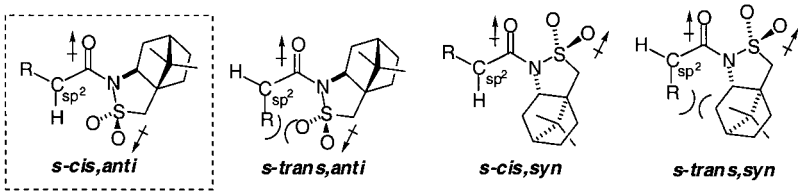
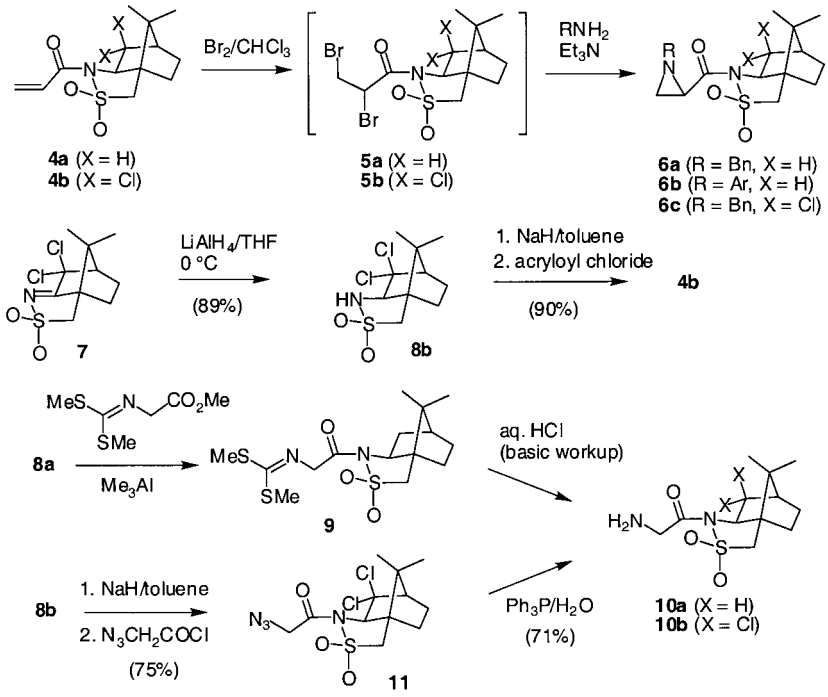


Figure 2. Possible conformations of carboxyl camphor sultams. Only the *s-cis*, *anti* conformer minimizes unfavorable dipole and steric interactions.

conformer. Although the need to incorporate a carboxylic acid into our dipole would seem to reduce the generality of this approach, we felt that any perceived limitation would be offset by the synthetic utility of this functional group. Such carbonyl-stabilized azomethine ylides[7] may be conveniently generated by thermolytic ring-opening of aziridine-2-carboxylic acid derivatives[8] or condensation of a glycine derivative with an aldehyde followed by tautomerization.[9]

The chiral aziridine-2-carboxamides **6a** and **6b** were prepared in high yield from the known (+)-*N*-propenoyl-bornane-2,10-sultam (**4a**, 'Oppolzer's sultam')[10] using a 2-step (1-pot) procedure (Scheme 1) which involved (1) alkene bromination (→**5**) followed by (2) double displacement by either benzylamine or *p*-anisidine to give **6a** and **6b**, respectively.[11] Although not relevant here, this aziridination is itself diastereoselective and can be used to prepare enantiomerically pure aziridine-2-carboxylic acid derivatives in high yields.[12] The 7,7-dichlorosultam aziridine **6c** was synthesized from the known compound **7**.[13] Treatment of **8b** with NaH and acryloyl chloride led to the clean formation of dichlorosultam **4b** in 90% yield. This contrasts with the same reaction on the unchlorinated sultam, where a considerable amount of the conjugate



Scheme 1.

Table 1. Dipolar cycloadditions of azomethine ylides generated by aziridine thermolysis

Entry	Azomethine ylide	Dipolarophile	Cycloadduct(s)	Stereoselectivity	Combined % yields
1	**6a**	**13**	**14a/15a**	8:1	60
2	**6b**	**13**	**14b/15b**	9:1	82
3	**6a**	**16**	**17a/18a/19a**	3:2:1	80
4	**6b**	**16**	**17b/18b/19b/20b**	10:8:3:1	93
5	**6c**	**16**	**18c/19c/20c**	4:1:1	91
6	**6a**	**21**	**22a/23a**	2:1	75
7	**6c**	**21**	**22c/23c**	4:1	84
8	**6a**	**25**	**26a/27a**	1:1	51
9	**6b**	**25**	**26b/27b/28b/29b**	4:4:1:1	92
10	**6c**	**25**	**27c/28c**	2:1	52[a]

[a] Unreacted starting material **6c** was recovered.

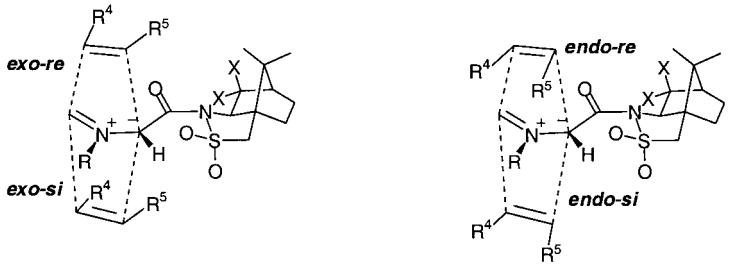
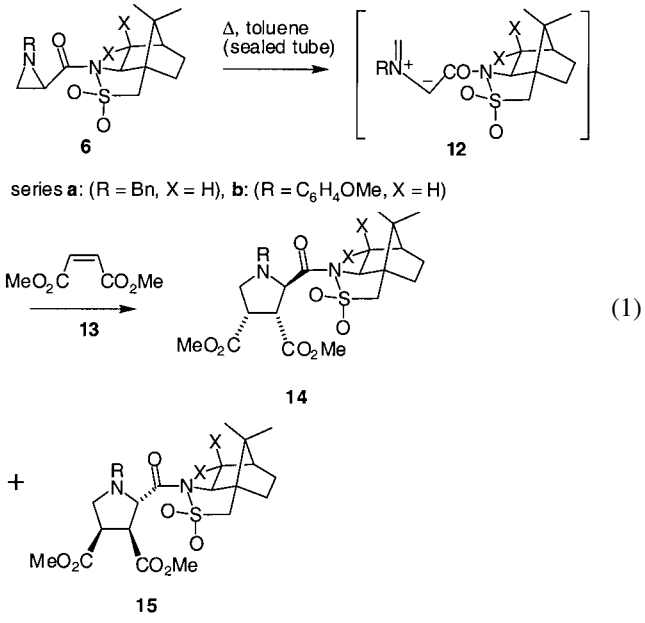


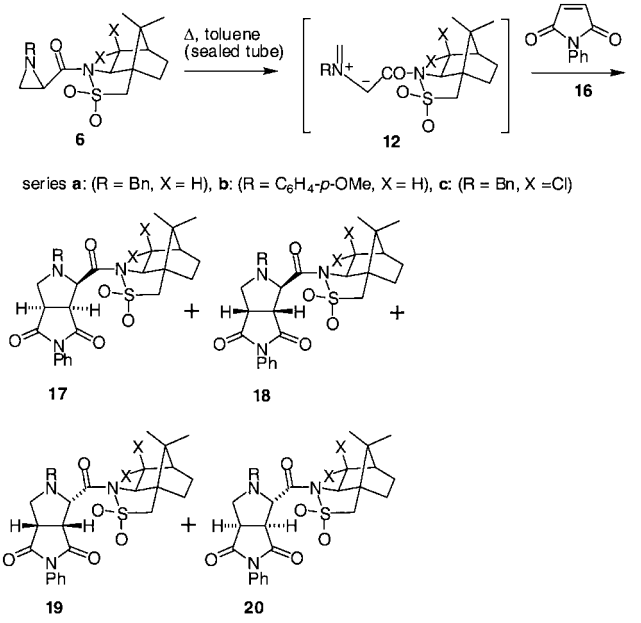
Figure 3. Competing diastereomeric transition states for the addition of azomethine ylide (**Z**)-**12** to the generic alkene dipolarophile **3**.

addition product was formed in addition to **4a**.[10b] By applying the aziridination procedure used for the synthesis of **6a** and **6b**, acryloyl dichlorosultam **4b** was readily converted to the corresponding aziridine **6c** in 74% yield. A variation of Oppolzer's published route to α-amino acids was used to synthesize the chiral glycyl sultam **10a**.[14] This method was not applicable to the synthesis of **10b** presumably due to the lower nucleophilicity of dichlorinated sultam. However, reaction of the anion of **8b** with azidoacetyl chloride gave **11** in 75% yield. Reduction of this compound using modified Staudinger conditions resulted in the clean formation of **10b** in 71% yield.



(1)

Upon thermolysis, aziridines **6a/b** underwent (presumed conrotatory) ring-opening to produce the corresponding *N*-substituted azomethine ylides which reacted with a variety of electron-deficient alkenes via 1,3-dipolar cycloaddition reactions (Table 1). With dimethyl maleate (**13**) as the dipolarophile, cycloadducts **14a** and **14b** were obtained as the major products (Eq. (1), entries 1 and 2 in Table 1) which conforms to exclusive *endo* cycloaddition to the *Z*-ylide **12a/b**. The *trans* orientation of H-2 and H-3 in these adducts was readily deduced in the 'b-series' where H-2 appeared as a singlet (dihedral angle=90°) in the ^{1}H NMR spectra of both **14b** and what we presume to be the minor facial diastereomer **15b**. The absolute stereochemistry of the major adducts conform to an *endo-re* TS (Fig. 3) that would be expected from the Oppolzer–Curran model. While the analogous 1,3-dipolar cycloadditions of **12a/b** to *N*-phenylmaleimide (**16**) occurred in good chemical yield, the *endo*-selectivity was considerably eroded with this dipolarophile (entries 3 and 4). The major products corresponded to bicyclic pyrrolidines **17a/b** (*exo-re*) and **18a/b** (*endo-re*), with former slightly predominating over the latter. Minor cycloadducts resulting from *si*-face addition (**19a/b**, and **20b**) were also isolated. The relative configuration of H-1 and H-6a in these cycloadducts was assigned by ^{1}H NMR as described above, with H-1 appearing as a doublet when they were *cis* to H-6a (**17** and **19**) and as a singlet when they are *trans* to H-6a (**18** and **20**) (Eq. (2)), in agreement with literature on similar compounds.[15]



(2)

Our stereochemical assignment for cycloadduct **17b** was unambiguously confirmed by X-ray crystallography (Fig. 4).[16] Interestingly, the cycloadduct corresponding to *exo-re* addition product **17** was not observed when the dichlorinated sultam auxiliary was employed (entry 5). We believe that steric hindrance caused by pro-S chlorine atom on the sultam disfavors *exo-re* addition to azomethine ylide **12c**. Thermolysis of aziridine **6a** in the presence of the unsymmetrical dipolarophile methyl acrylate (**21**) led to the formation of regioisomeric adducts **22a** and **23a** in a ratio of 2:1 (Eq. (3), entry 6). The regiochemistry of these adducts were easily deduced from the splitting pattern of H-2 (d in **22a** versus dd in **23a**). The stereochemistry of **22a** was

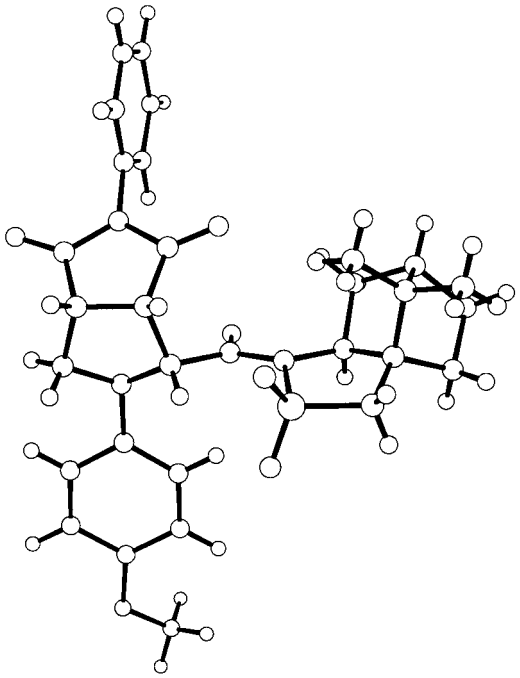
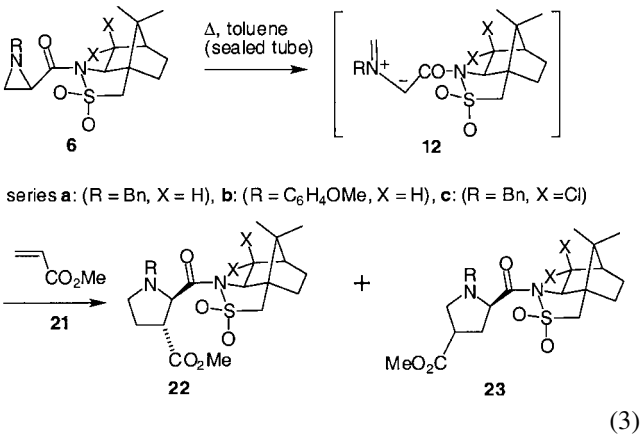


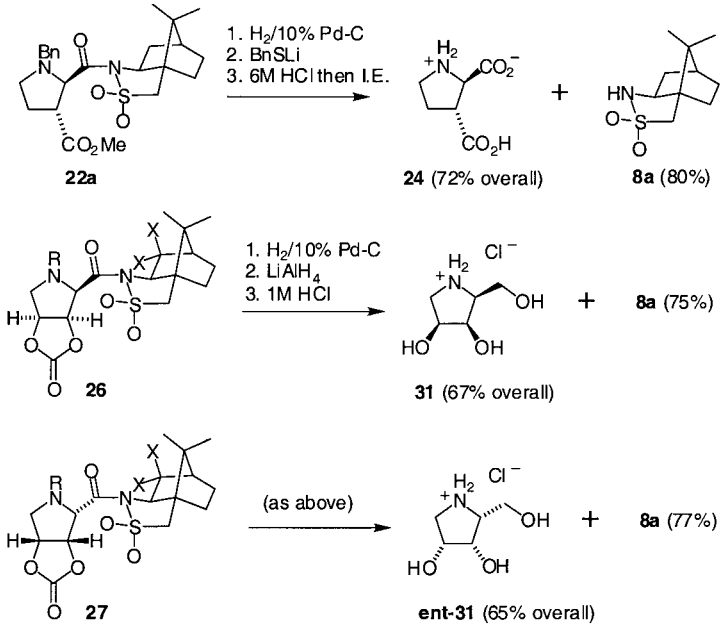
Figure 4. X-Ray crystal structure of cycloadduct **17b**.

established by its conversion to and correlation with the known[17] pyrrolidine dicarboxylic acid **24** (Scheme 2). Note that the auxiliary was recovered from this reaction in high yield. These thiolate-mediated cleavage conditions were necessary because the usual reagents (LiOH, LiOOH) were found to attack the sulfoxide moiety preferentially.[18]



(3)

Repetition of the dipolar cycloaddition sequence with the dichloroaziridine **6c** resulted in a doubling of the regioselectivity to 4:1 (entry 7). It should be noted that the poor *endo*/*exo* and regioselectivity associated with dipolarophiles **16** and **21** mirror Tsuge's observations with related (achiral) *N*-substituted azomethine ylides. Finally, we also examined the thermolysis of aziridines **6a–c** in the presence of vinylene carbonate **25** (Eq. (4), entries 8–10). With *N*-benzylaziridine **6a**, two major cycloadducts identified as **26a** and **27a** were isolated in equimolar quantities, along with a significant amount of a pyrrole **30a** and free sultam **8a**. All 4 possible cycloadducts **26b–29b** (ratio=4:4:1:1) were obtained in excellent yield in the noticeably more reactive *N*-aryl series without any by-products. Once again, ^{1}H NMR analysis allowed assignment of relative stereochemistry of the pyrrolidine moiety. The structures of **26a** and **27a** were established by separately converting them to known



Scheme 2.

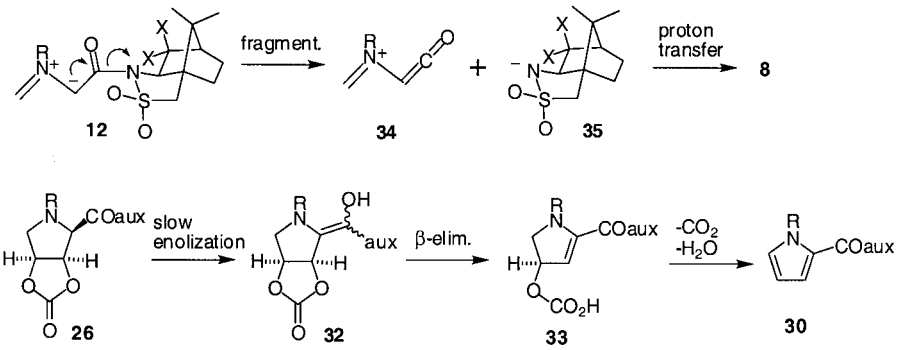
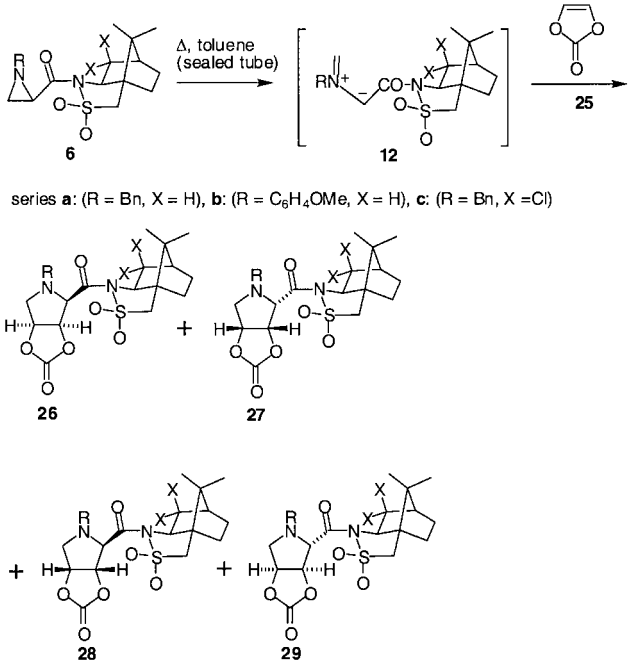


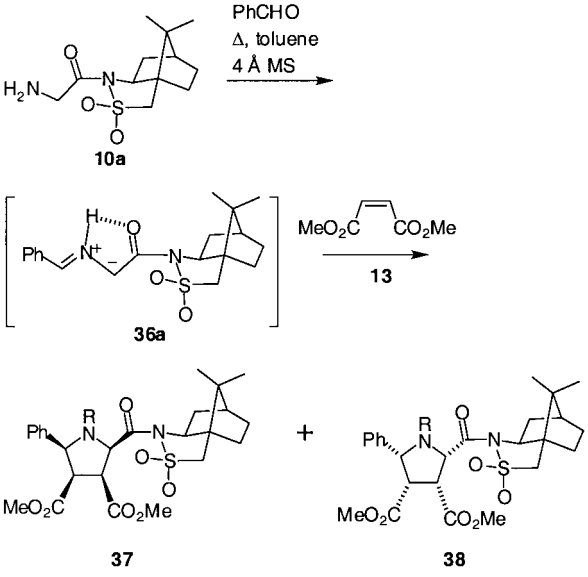
Figure 5. Formation of by-products **8** and **30**.

compounds **31**[3g] and **ent-31**[19] (Scheme 2). A control experiment showed that free sultam **9** can arise from extended thermolysis of **6a** in the absence of dipolarophile (Fig. 5).



(4)

Apparently, dipolar cycloaddition to the electron-rich **25** is slow enough to allow this decomposition pathway to intervene here. The formation of pyrrole **30a** presumably occurs via slow, reversible enolization followed by a fast elimination/decarboxylation sequence. Enolization of an initially formed *endo-re* cycloadduct **26** would account for our obtaining '*exo-si*' **27** as a major product without the need to abandon the Oppolzer–Curran TS model. The reaction of chlorinated aziridine **6c** with **25** apparently underwent selective formation of *endo-re* cycloadduct **28** (recall entry 5) which then undergoes epimerization to **27** and decomposition to **30c**.



(5)

We also examined 1,3-dipolar cycloadditions of chiral azomethine ylides generated from the glycyl sultams **10a–b** and benzaldehyde using the 'imine tautomerization route' of Tsuge (Table 2). With dipolarophile **13**, parent sultam auxiliary gave cycloadducts **37a** and **38a** in good yield and the usual selectivity (Eq. (5), entry 1). Two other minor compounds, which may be the remaining diastereomers, could be detected in the crude ^{1}H NMR

Table 2. Dipolar cycloadditions of azomethine ylides generated by imine tautomerization

Entry	Azomethine ylide	Dipolarophile	Cycloadduct(s)	Stereoselectivity	Combined % yields
1	**36a**	**13**	**37/38**	7:1	66[a]
2	**36a**	**16**	**39a/40a**	8:1	84
3	**36b**	**16**	**39b/40b/41b**	1:2:1	64
4	**36a**	**21**	**42a/43a**	5:1	64
5	**36b**	**21**	**42b/43b**	8:1	58

[a] Two other minor diastereomers detected in the crude ^{1}H NMR spectrum.

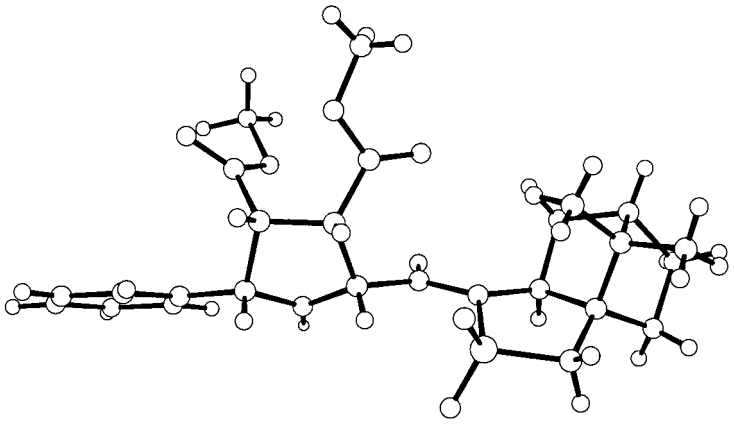
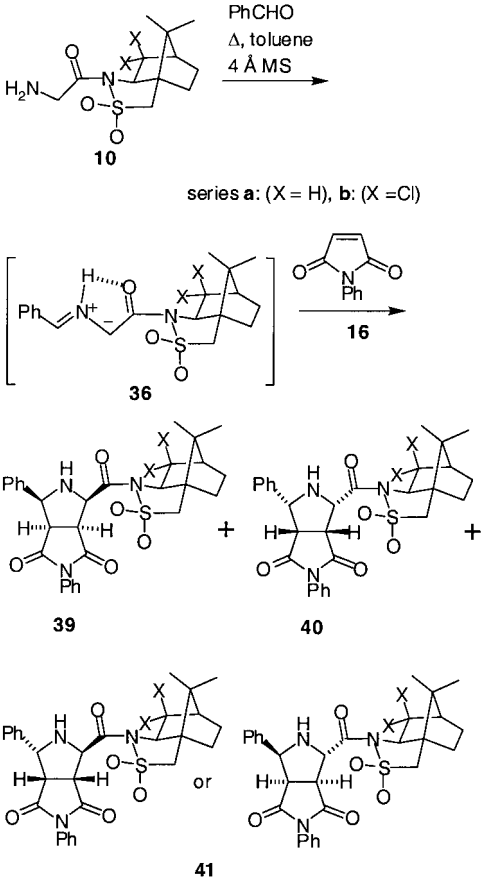


Figure 6. X-ray crystal structure of cycloadduct **37a**.

spectrum. Free sultam **8a**, which may form via azomethine ylide decomposition or hydrolysis by the liberated H_2O, was also isolated in 15% yield. The absolute stereochemistry of the major cycloadduct **37a** was unambiguously established by X-ray crystallography (Fig. 6) and showed that all the pyrrolidine substituents were *cis* to each other. This cycloadduct was clearly the result of *endo-re* addition of the dipolarophile to the (*E*,*E*)-ylide **36a**. Dipolar cycloaddition of **36a** to *N*-phenylmaleimide (**16**) (Eq. (6)) gave a good yield of cycloadducts **39a** and **40a** in a ratio of 8:1 (entry 2). These adducts presumably arose from *endo-re* and *endo-si* addition to **36a**. Once again, a small amount of the free sultam **8a** (5%) was isolated. The relative pyrrolidine stereochemistry was readily deduced from their ^{1}H NMR spectra in which H-1 and H-3 appeared as doublets, indicating the *cis* arrangement of these protons relative to H-6a and H-3a respectively. This assignment was further confirmed by NOE experiments on **39a**, wherein irradiation of H-1 resulted in enhancement of H-3 (8%) and H-6a (16%). Conversely, irradiation of H-3 resulted in enhancement of H-1 (8%) and H-3a (21%). When this cycloaddition was performed using the dichlorinated glycyl sultam 10b (entry 3), the diastereomer **40b** was favored and the ratio of **40b/39b** dropped to 2:1. A new product tentatively identified as **41b** was isolated as well in addition to free sultam **8b** (20%). The relative stereochemistry of the pyrrolidine in **41b** was evident from its ^{1}H NMR spectrum, where H-1 appeared as a singlet and H-3 as a doublet. Formation of this cycloadduct was rather unexpected but must occur via epimerization of either **39b** or **40b** or (less likely) by addition to the (*Z*,*E*) isomer of ylide **36b** (not shown). Finally, when unsymmetrical dipolarophile **21** was used with both sultam auxiliaries (Eq. (7)), good yields of cycloadducts corresponding to **42** and **43** were isolated in the usual selectivities (5:1 and 8:1, respectively) along with minor amounts of free sultam (entries 4 and 5). Both the regiochemistry and relative stereochemistry of these cycloadducts were easily determined by the characteristic upfield shift of the 3-CO_2Me ^{1}H NMR signal due to the shielding effect of the *cis*-2-phenyl group. Once again, it is assumed that the major product results from *endo-re* addition to the corresponding azomethine ylide **36** in accord with the Oppolzer–Curran TS model.

In conclusion, we have shown that Oppolzer's sultam can serve as an effective, recoverable chiral auxiliary for stabilized azomethine ylides generated by aziridine thermolysis and imine tautomerization. These chiral azomethine ylides undergo 1,3-dipolar cycloadditions with a variety of dipolarophiles to give good yields of diastereomerically enriched cycloadducts. Subsequent removal of the chiral auxiliary provides access to a variety of enantiomerically pure pyrrolidine derivatives.



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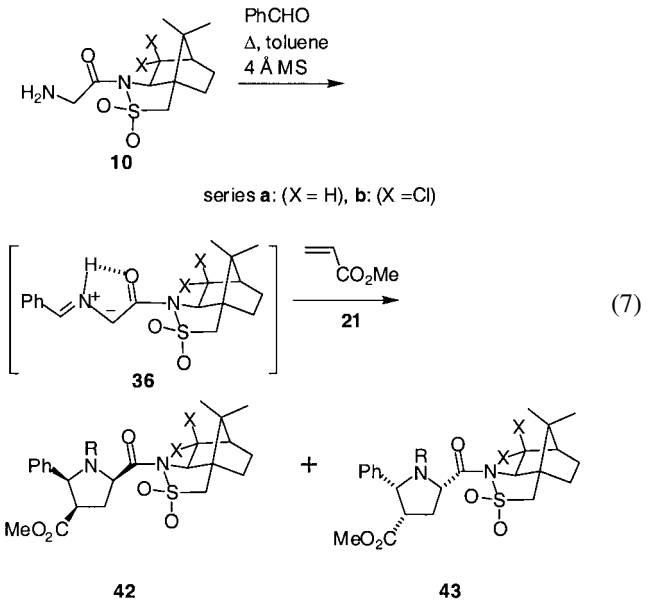

(7)

3. Experimental

All reactions were carried out in oven- or flame-dried glassware under Ar or N_2 atmosphere unless otherwise stated. Solvents and reagents were purified and dried beyond commercial reagent grade as follows: THF, benzene, and toluene were distilled from Na/benzophenone under N_2. $CHCl_3$, CH_2Cl_2, 1,2-dichloroethane, MeCN, DMF, and Et_3N were distilled from CaH_2. Analytical (preparative) TLC was performed on E. Merck 0.25 (0.5) mm precoated silica gel 60 F-254 and visualized with UV illumination followed by charring with either 5% anisaldehyde in (95:5:1) EtOH–AcOH–H_2SO_4 (char A) or 0.3% ninhydrin in (97:3) *n*-BuOH–AcOH (char B). Flash chromatography was carried out using E. Merck silica gel 60 (230–400 mesh). Analytical normal and reverse phase HPLC were performed using Dynamax-60A 8 μm silica gel and C-18 columns (4.6 mm internal diameter) respectively. Preparative HPLC separations were performed using columns with a 21.4 mm internal diameter. Melting points are uncorrected. Optical rotations were measured at λ=589 nm (sodium D line) at room temperature and were reported as follows: $[\alpha]_D$ (concentration, *c* in g/100 mL, solvent). ^{1}H NMR spectra were recorded at either 200 or 300 MHz and are reported in parts per million (ppm) on the δ scale relative to residual $CHCl_3$ (δ 7.25), C_6D_5H (δ 7.15), TMS (δ 0.00) or HDO (δ 4.63). ^{13}C NMR spectra were acquired at 75 MHz and are reported in parts per million (ppm) on the δ scale relative to $CHCl_3$ (δ 77.00). The NMR experiments were performed at room temperature unless otherwise indicated. ^{1}H NMR signal assignments[20] were based on the selective homonuclear decoupling experiments. High resolution mass (HRMS) data were reported for M^+ or the highest mass fragment derived from M^+ in electron impact (EI) mode. Fast atom bombardment ionization (FAB) was performed on samples in a glycerol matrix.

3.1. [3a*R*-(3aα,6α,7aβ)]-3*H*-3a,6-Methano-2,1-benzisothiazole, 7,7-dichloro-4,5,6,7-tetrahydro-8,8-dimethyl-2,2-dioxide (8b)

A solution of dichloroimine **7** (7.81 g, 27.7 mmol) in THF (100 mL) was added to a stirring suspension of $LiAlH_4$ (1.00 g, 27.7 mmol) in THF (20 mL) at 0°C. The reaction mixture was stirred at this temperature until judged complete by TLC (less than 1 h) then hydrolyzed by slow addition of 1.0N HCl over 2 h. The resulting suspension was diluted with THF (100 mL), filtered and the aqueous phase was extracted with $CHCl_3$ (2×100 mL). The combined organic phase was dried over $MgSO_4$, filtered and concentrated to give crude sultam. This was recrystallized from EtOH to give 6.40 g (89%) of **8b** as a white solid. R_f 0.64 (1:1 hexanes/EtOAc); mp=203–204°C; $[\alpha]_D^{25}$=−19° (*c*=1.3, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 4.93 (br s, 1H, N–H), 3.94 (d, *J*=5.6 Hz, 1H, H-2), 3.22 (s, 2H, CH_2SO_2), 2.54 (d, *J*=4.7 Hz, 1H), 2.32 (1H), 2.10–1.85 (2H), 1.62 (1H), 1.45 (s, 3H, CH_3), 1.04 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$) δ 93.4, 77.3, 61.6, 56.1, 50.4, 49.8, 30.3, 25.8, 23.3, 23.0; IR ($CHCl_3$) cm^{-1} 3000 (s), 1320 (s), 1210 (s), 1140 (s), 750 (s); HRMS calcd for $C_{10}H_{15}NO_2SCl_2$ (M^+) 283.0201, found 283.0201.

3.2. [3a*R*-(3aα,6α,7aβ)]-7,7-Dichloro-4-5,6,7-tetrahydro-8,8-dimethyl-1-(1-oxo-2-propenyl)-3*H*-3a,6-methano-2,1-benzisothiazole 2,2-dioxide (4b)

To a stirred suspension of NaH (0.73 g, 30.31 mmol, 60% dispersion in mineral oil) in toluene (10 mL) was added sultam **8b** (5.90 g, 20.8 mmol) in toluene (120 mL) under N_2 atmosphere at rt. After stirring for 30 min at the same temperature, acryloyl chloride (3.36 mL, 41.5 mmol) was added and the stirring continued for 1 h. At this point, the reaction was judged complete by TLC. The mixture was cooled to 0°C, quenched with water and the organic phase was separated. The aqueous phase was extracted with EtOAc (2×50 mL), and the combined organic phase was dried over $MgSO_4$, filtered and concentrated to give crude acryloyl sultam which was recrystallized from EtOH to give 6.32 g (90%) of **4b** as a white solid. R_f 0.67 (4:1 benzene/EtOAc); mp=213–214°C; $[\alpha]_D^{25}$= +13° (*c*=2.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 6.84 (dd, *J*=16.7, 10.2 Hz, 1H, H-β), 6.63 (d, *J*=17.0 Hz, 1H, H′-β), 5.97 (d *J*=11.2 Hz, 1H, H-α) 4.51 (s, 1H, H-2), 3.56 (d, *J*=13.7 Hz, 1H, 1/2CH_2SO_2), 3.50 (d, *J*=13.7 Hz, 1H, 1/2CH_2SO_2), 2.58 (d, *J*=4.4 Hz, 1H), 2.45 (1H), 2.10–1.92 (2H), 1.62 (1H), 1.50 (s, 3H, CH_3), 1.11 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$) δ 165.3, 132.7, 127.6, 93.5, 78.6, 62.1, 52.3, 50.6, 49.6, 31.6, 25.4, 24.2, 23.0; IR ($CHCl_3$) cm^{-1} 3010 (s), 1700 (s), 1620 (w), 1400 (s), 1340 (s), 1215 (s), 1140 (m), 1070 (m), 985 (m); HRMS calcd for $C_{13}H_{17}NO_3SCl_2$ (M^+) 337.0306, found 337.0302.

3.3. [3a*R*-[1(*S**),3aα,6α,7aβ]]-3*H*-3a,6-Methano-2,1-benzisothiazole, 7,7-dichloro-4-5,6,7-tetrahydro-8,8-dimethyl-1-[[1-(phenylmethyl)-2-aziridinyl]carbonyl]-2,2-dioxide (6c)

Liquid bromine (1 equiv.) was added to a stirring solution of acryloyl sultam **4c** (1 equiv.) in $CHCl_3$ (spectroscopic grade, concentration approx. 0.3 M) under an Ar/N_2 atmosphere.

After stirring at ~50°C for 1 h, Et_3N (2 equiv.) and benzylamine (1.5 equiv.) were added to the reaction flask and stirring was continued at ~50°C overnight. At this time, the reaction was judged complete by TLC, and so was diluted with $CHCl_3$. The organic layer was washed successively with 0.1N HCl, sat. $NaHCO_3$ soln., brine, and dried ($MgSO_4$). Evaporation of the solvent and purification of the residue by recrystallization from EtOAc gave the desired aziridine **6c** in 74% yield; R_f 0.23 ($CHCl_3$); mp=240–241°C; $[\alpha]_D^{22}=-27°$ (c=0.73, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 7.40–7.20 (5H, Ph), 4.42 (s, 1H, H-7a), 3.86 (d, J=13.5 Hz, 1H, 1/2 H_2Ph), 3.51 (d, J=13.7 Hz, 1H, 1/2CH_2SO_2), 3.45 (d, J=13.8 Hz 1H, 1/2CH_2SO_2), 3.40 (d, J=13.6 Hz, 1H, 1/2CH_2Ph), 2.78 (dd, J=6.3, 3.1 Hz, 1H, H-2), 2.51 (d, J=4.4 Hz, 1H, H-3), 2.46–2.36 (2H), 2.40–1.88 (3H), 1.55 (1H), 1.41 (s, 3H, CH_3), 1.08 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$) δ 173.0, 137.9 (2C) 128.3, 128.2 (2C), 127.2, 103.4, 78.4, 63.8, 62.1, 52.7, 50.9, 49.6, 38.3, 36.7, 31.6, 25.4, 24.2, 22.9; IR ($CHCl_3$) cm^{-1} 3010 (m), 1725 (s), 1410 (s), 1340 (s), 1215 (s), 1140 (m), 1060 (m); HRMS calcd for $C_{20}H_{24}N_2O_3SCl_2$ (M^+) 442.0885, found 442.0885.

3.4. *N*-(2′-Aminoacetyl)bornane-2,10-sultam (10b)

To a stirring suspension of sultam **8b** (500 mg, 1.76 mmol) and NaH (130 mg, 1.84 mmol, 60% oil dispersion) in dry toluene (19 mL) was added azidoacetyl chloride (525 mg, 4.40 mmol) and the resulting mixture was stirred 3 h, whereupon TLC analysis indicated complete consumption of **8b**. The reaction mixture was cooled in an ice bath and hydrolyzed by slow addition of water. The aqueous layer was separated, extracted with CH_2Cl_2 (2×25 mL), dried ($MgSO_4$), and concentrated to give crude azide which was purified by flash chromatography on silica gel (2:1 hexanes/EtOAc) to give **11** in 75% yield. R_f 0.5 (1:1 hexanes/EtOAc); ^1H NMR ($CDCl_3$) δ 4.50 (d, J=16.8 Hz, 1H, H-7a), 4.47 (s, 1H, H-2), 4.23 (d, J=17.2 Hz, 1H, H-7a′), 3.53 (s, 2H, CH_2SO_2), 2.59 (d, J=4.51 Hz, 1H), 2.45 (1H), 2.12–1.93 (2H), 1.68–1.54 (1H), 1.46 (s, 3H, CH_3), 1.10 (s, 3H, CH_3). **10b**: To a stirred solution of **11** (450 mg, 1.23 mmol) in THF (20 mL) was added PPh_3 (322 mg, 1.23 mmol) and H_2O (0.05 mL). After stirring the mixture at room temperature for 30 h, TLC analysis showed complete consumption of **10**. The mixture was then diluted with THF (20 mL), and HCl (0.2N, 5 mL) was added. The aqueous layer was separated, extracted with EtOAc (2×15 mL), then neutralized with saturated $NaHCO_3$ and further extracted with CH_2Cl_2 (5×25 mL). The combined organic layers were dried ($MgSO_4$), and concentrated to give 297 mg (71%) of **11b**. R_f 0.15 (1:1 hexanes/EtOAc); ^1H NMR ($CDCl_3$) δ 4.43 (s, 1H, H-2), 4.06 (d, J=18.2 Hz, 1H, H-7a), 3.76 (d, J=18.2 Hz, 1H, H-7a′), 3.50 (s, 2H, CH_2SO_2), 2.57 (d, J=4.5 Hz, 1H), 2.42 (1H), 2.10–1.90 (2H), 1.60 (2H), 1.46 (s, 3H, CH_3), 1.09 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$) δ 132.0, 128.6, 93.4, 78.6, 62.1, 52.4, 50.4, 49.6, 31.6, 30.4, 25.4, 24.1; IR ($CHCl_3$) cm^{-1} 3010 (m), 2960 (m), 1710(s), 1340 (s),1270 (s), 1220 (s), 1130 (s), 1050 (m) HRMS calcd for $C_{10}H_{15}NO_2SCl_2$ ([M−$COCHNH_2$]$^+$) 283.0200, found 283.0187.

3.5. General procedure for aziridine thermolyses

The starting aziridine and dipolarophile (3 equiv.) were dissolved in toluene (concentration approx. 0.3 M) and sealed in a 5 mL Pyrex tube after degassing. The sealed tube was heated for the reported period of time (refer to individual experiments below). The tube was then cooled, carefully broken open, and the contents concentrated. The crude reaction mixture was analyzed by ^1H NMR then subjected to chromatographic purification.

3.5.1. [3a*R*-[1(2*R,3*R**,4*S**),3aα,6α,7aβ]]-3,4-Pyrrolidinedicarboxylic acid, 1-(phenylmethyl)-2-[(tetrahydro-8,8-dimethyl-3*H*-3a,6-methano-2,1-benzisothiazol-1(4*H*)-yl)carbonyl]-dimethyl ester, *S*,*S*-dioxide (14a).** Reaction time: 6 h; temperature 195–205°C; flash chromatography (SiO_2, 3:1 hexanes/EtOAc, further purification was accomplished by PTLC on silica gel, eluting twice); total yield of the cycloadducts 60%; R_f 0.26 (2:1 hexanes/EtOAc); mp=51–53°C; $[\alpha]_D^{22}=+82°$ (c=0.88, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 7.36–7.26 (5H, Ph), 4.41 (d, J=4.5 Hz, 1H, H-2), 3.96 (d, J=13.3 Hz, 1H, 1/2CH_2Ph), 3.96 (dd, J=7.4, 4.6 Hz, 1H, H-7a), 3.68 (s, 3H, OCH_3), 3.63 (s, 3H, OCH_3), 3.65 (d, J=13.3 Hz, 1H, 1/2CH_2Ph), 3.50 (d, J=13.7 Hz, 1H, 1/2CH_2SO_2), 3.43 (d, J=13.8 Hz, 1H, 1/2CH_2SO_2), 3.38 (dd, J=14.5, 2.2 Hz, 1H, H-5), 3.29 (dd, J=8.9, 4.6 Hz, 1H, H-3), 3.21 (t, J=8.1 Hz, 1H, H-4), 2.97 (t, J=9.3 Hz, 1H, H-5), 2.20–1.80 (5H), 1.30–1.47 (2H), 1.17 (s, 3H, CH_3), 0.97 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$) δ 172.1, 171.8, 171.5, 138.6, 128.8 (2C), 128.3 (2C), 127.1, 68.5, 65.3, 57.7, 53.5, 53.23, 52.3, 52.0, 50.6, 48.6, 47.8, 45.4, 44.7, 38.3, 32.9, 26.5, 20.8, 19.9; IR ($CHCl_3$) cm^{-1} 3670 (w), 3010 (m), 2950 (w), 2380 (w), 1740 (s, C=O), 1430 (w), 1330 (m), 1265 (s), (1215 (s), 1130 (m); HRMS calcd for $C_{26}H_{34}N_2O_7S$ (M^+) 519.2165, found 519.2168.

3.5.2. [3a*R*-[1(2*S,3*S**,4*R**),3aα,6α,7aβ]]-3,4-Pyrrolidinedicarboxylic acid, 1-(phenylmethyl)-2-[(tetrahydro-8,8-dimethyl-3*H*-3a,6-methano-2,1-benzisothiazol-1(4*H*)-yl)carbonyl]-dimethyl ester, *S*,*S*-dioxide (15a).** R_f 0.26 (2:1 hexanes/EtOAc); ^1H NMR ($CDCl_3$) δ 7.40–7.20 (5H, Ph), 4.42 (d, J=3.2 Hz, 1H, H-2), 4.00 (d, J=13.4 Hz, 1H, 1/2CH_2Ph), 3.83 (d, J=13.4 Hz, 1H, 1/2CH_2Ph), 3.71 (s, 3H, OCH_3), 3.65 (s, 3H, OCH_3), 3.65 (dd, J=6.0, 3.0 Hz, 1H, H-7a), 3.56 (dd, J=9.1, 7.7 Hz, 1H, H-5), 3.50 (dd, J=8.2, 3.4 Hz, 1H, H-3), 3.44 (d, J=13.8 Hz, 1H, 1/2CH_2SO_2), 3.37 (d, J=13.8 Hz, 1H, 1/2CH_2SO_2), 3.30 (1H, dd, J=8.9, 7.3 Hz, H-4), 3.10 (1H, t, J=9.2 Hz, H-5), 2.10–1.80 (5H, m), 1.40–1.20 (2H, m), 0.93 (3H, s, CH_3), 0.92 (3H, s, CH_3); ^{13}C NMR ($CDCl_3$) δ 172.4, 172.1, 171.7, 138.7, 128.7 (2C), 128.4 (2C), 127.2, 67.2, 65.4, 58.3, 54.6, 53.1, 52.4, 52.0, 49.9, 45.6, 47.7, 45.5, 44.8, 38.6, 33.0, 26.4, 21.1, 19.9.

3.5.3. [3a*R*-[1(2*R,3*R**,4*S**),3aα,6α,7aβ]]-3,4-Pyrrolidinedicarboxylic acid, 1-(4-methoxyphenyl)-2-[(tetrahydro-8,8-dimethyl-3*H*-3a,6-methano-2,1-benzisothiazol-1(4*H*)-yl)carbonyl]-dimethyl ester, *S*,*S*-dioxide (14b).** Reaction time: 6 h; temperature 195–205°C; flash chromatography (SiO_2, 2:1 hexanes/EtOAc); total yield of the cycloadducts 82%; (isolated as a 9/1 mixture); R_f 0.13 (2:1 hexanes/EtOAc); $[\alpha]_D^{23}=+14°$ (c=4.0, $CHCl_3$); ^1H NMR (C_6D_6) δ 6.95–6.86 (4H, arom.), 5.82 (s, 1H, H-2), 4.21 (t, J=8.9 Hz, 1H, H-4), 3.88 (t, J=8.6 Hz, 1H, H-5), 3.79 (d, J=7.2 Hz, 1H, H-3), 3.65 (dt, J=9.1, 2.0 Hz, 1H, H-5), 3.47 (dd,

J=5.9, 2.8 Hz, 1H, H-7a), 3.37 (s, 3H, OCH_3), 3.53 (s, 3H, OCH_3), 3.30 (s, 3H, OCH_3), 2.77 (d, J=13.9 Hz, 1H, 1/2CH_2SO_2), 2.70 (d, J=13.9 Hz, 1H, 1/2CH_2SO_2), 1.91 (1H), 1.78 (dd, J=7.9, 6.0 Hz, 1H), 1.29 (3H), 1.22–1.10 (1H), 0.94 (s, 3H, CH_3), 0.75–0.50 (2H), 0.37 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$) δ 171.1, 170.6, 151.0, 140.1, 115.1 (2C), 113.2, 113.1 (2C), 66.3, 64.7, 55.9, 52.9, 52.8, 52.3, 48.9, 48.2, 48.0, 48.0, 44.5, 43.7, 38.3, 37.3, 26.4, 21.0, 19.9; IR ($CHCl_3$) cm^{-1} 3680 (w), 3010 (m), 2950 (w), 2480 (w), 1735 (s, C=O), 1695 (m), 1510 (s), 1430 (m), 1330 (s), 1260 (s), (1215 (s), 1125 (m), 1030 (m); HRMS calcd for $C_{26}H_{34}N_2O_8S$ (M^+) 535.2114, found 535.2085.

3.5.4. [3a*R*-[1(1*R,3a*R**,6a*S**),3aα,6α,7aβ)]]-3*H*-3a,6-Methano-2,1-benzisothiazole, hexahydro-8,8-dimethyl-1-[[octahydro-4,6-dioxo-5-phenyl-2-(phenylmethyl)pyrrolo[3,4-*c*]-pyrrol-1-yl]carbonyl]-2,2-dioxide (17a).** Reaction time: 15 h; temperature 167–170°C; flash chromatography (SiO_2, 3:1 hexanes/EtOAc); total yield of the cycloadducts 80%; R_f 0.35 (2:1 hexanes/EtOAc); mp=287–289°C; $[\alpha]_D^{24}$=+108° (c=1.94, $CHCl_3$); ^{1}H NMR (C_6D_6) δ 7.42 (d, J=8.2, 2H, Ph), 7.38 (d, J=8.2, 2H, Ph), 6.90 (6H, Ph), 4.31 (d, J=7.6 Hz, 1H, H-1), 4.29 (d, J=12.8 Hz, 1H, 1/2CH_2Ph), 3.68 (dd, J=7.8, 4.7 Hz, 1H, H-7a), 3.48 (t, J=8.1 Hz, 1H, H-6a), 3.31 (d, J=9.5 Hz, 1H, H-3), 3.24 (d, J=13.1 Hz, 1H, 1/2CH_2Ph), 2.92 (d, J=13.8 Hz, 1H, 1/2CH_2SO_2), 2.79 (d, J=13.8 Hz, 1H, 1/2CH_2SO_2), 2.77 (1H), 2.43 (t, J=7.9 Hz, 1H, H-3a), 1.91 (dd, J=14.0, 7.9 Hz, 1H), 1.83 (dd, J=9.7, 7.7 Hz, H-3), 1.47 (s, 3H, CH_3), 1.40–1.25 (2H), 1.15 (1H), 0.79 (1H), 0.63 (1H), 0.49 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$) δ 177.4, 175.4, 167.4, 137.6, 132.0, 129.3 (2C), 128.8, 128.4 (2C), 128.4 (2C), 127.4, 126.8 (2C), 68.9, 65.8, 56.7, 54.6, 53.4, 48.8, 48.0, 44.6, 43.8, 37.5, 32.9, 26.7, 20.5, 20.1; IR ($CHCl_3$) cm^{-1} 3660 (w), 3000 (m), 2950 (w), 2380 (w), 1710 (s, C=O), 1490 (w), 1380 (m), 1320 (m), 1265 (m), 1200 (s), 1125 (m); HRMS calcd for $C_{19}H_{17}N_2O_3$ ([M−$C_{11}H_{16}NO_3S$]$^+$) 305.1289, found 305.1292.

3.5.5. [3a*R*-[1(1*R,3a*S**,6a*R**),3aα,6α,7aβ)]]-3*H*-3a,6-Methano-2,1-benzisothiazole, hexahydro-8,8-dimethyl-1-[[octahydro-4,6-dioxo-5-phenyl-2-(phenylmethyl)pyrrolo[3,4-*c*]-pyrrol-1-yl]carbonyl]-2,2-dioxide (18a).** To separate this cycloadduct from **17a**, a second flash chromatography eluting with 5:1 benzene/EtOAc, was necessary; R_f 0.28 (5:1 benzene/EtOAc); $[\alpha]_D^{23}$=+37° (c=2.4, $CHCl_3$); ^{1}H NMR (C_6D_6, 70°C) δ 7.40 (d, J=8.1 Hz, 2H, Ph), 7.24–6.95 (8H, Ph), 4.82 (br s, 1H, H-1), 4.11 (d, J=13.2 Hz, 1H, 1/2CH_2Ph), 3.91 (d, J=13.2 Hz, 1H, 1/2CH_2Ph), 3.72 (dd, J=7.8, 4.8 Hz, 1H, H-7a), 3.25 (d, J=9.5 Hz, 1H, H-3), 3.11 (d, J=8.4 Hz, 1H, H-6a), 2.97 (t, J=8.4 Hz, 1H, H-3a), 2.88 (d, J=13.7 Hz, 1H, 1/2CH_2SO_2), 2.76 (d, J=13.7 Hz, 1H, 1/2CH_2SO_2), 1.81 (dd, J=9.5, 8.3 Hz, 1H, H-3), 1.45–1.15 (4H), 1.08 (s, 3H, CH_3), 0.90–0.70 (3H), 0.49 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$) δ 177.6, 175.5, 171.1, 138.3, 132.2, 129.1 (2C), 128.7, 128.5 (2C), 128.4 (2C), 127.3, 126.4 (2C), 65.8, 64.5, 54.3, 53.8, 52.7, 49.5, 49.1, 47.9, 45.0, 44.4, 38.4, 33.1, 26.3, 21.0, 19.9; IR ($CHCl_3$) cm^{-1} 3670 (w), 3010 (m), 2960 (w), 2380 (w), 1710 (s, C=O), 1490 (w), 1370 (m), 1335 (m), 1260 (m), 1200 (s), 1160 (m), 1125 (m); HRMS calcd for $C_{19}H_{18}N_2O_3$ ([M−$C_{11}H_{15}NO_3S$]$^+$) 306.1368, found 306.1357.

3.5.6. [3a*R*-[1(1*S,3a*S**,6a*R**),3aα,6α,7aβ)]]-3*H*-3a,6-Methano-2,1-benzisothiazole, hexahydro-8,8-dimethyl-1-[[octahydro-4,6-dioxo-5-phenyl-2-(phenylmethyl)pyrrolo[3,4-*c*]-pyrrol-1-yl]carbonyl]-2,2-dioxide (19a).** R_f 0.41 (5:1 benzene/EtOAc); $[\alpha]_D^{23}$=+18° (c=1.1, $CHCl_3$); ^{1}H NMR (C_6D_6) δ 7.63 (d, J=8.8 Hz, 2H, arom.), 7.27 (d, J=8.8 Hz, 2H, arom.), 7.05–6.90 (6H, Ph), 4.29 (d, J=8.7 Hz, 1H, H-1), 3.86 (d, J=13.3 Hz, 1H, 1/2CH_2Ph), 3.85 (1H, H-7a), 3.75 (t, J=8.4 Hz, 1H, H-6a), 3.36 (d, J=9.7 Hz, 1H, H-3), 3.32 (d, J=13.4 Hz, 1H, 1/2CH_2Ph), 2.86 (d, J=13.8 Hz, 1H, 1/2CH_2SO_2), 2.78 (d, J=13.7 Hz, 1H, 1/2CH_2SO_2), 2.42 (t, J=7.4 Hz, 1H, H-3a), 2.05–1.85 (3H), 1.40–1.18 (3H), 1.05 (s, 3H, CH_3), 0.70 (1H), 0.50 (1H), 0.50 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$) δ 177.5, 175.7, 168.2, 136.5, 132.1, 129.2 (2C), 128.9 (2C), 128.6, 128.5 (2C), 127.6, 126.8 (2C), 68.4, 66.1, 56.4, 54.0, 53.3, 48.8, 47.91, 45.0, 44.3, 38.9, 32.9, 29.8, 26.3, 21.3, 19.9; IR ($CHCl_3$) cm^{-1} 3010 (m), 1710 (s, C=O), 1490 (w), 1370 (m), 1335 (m), 1260 (m), 1200 (s), 1125 (m); HRMS calcd for $C_{19}H_{17}N_2O_3$ ([M−$C_{11}H_{16}NO_3S$]$^+$) 305.1289, found 305.1273.

3.5.7. [3a*R*-[1(1*R,3a*R**,6a*S**),3aα,6α,7aβ)]]-3*H*-3a,6-Methano-2,1-benzisothiazole, hexahydro-8,8-dimethyl-1-[[octahydro-4,6-dioxo-5-phenyl-2-(4-methoxyphenyl)pyrrolo-[3,4-*c*]pyrrol-1-yl]carbonyl]-2,2-dioxide (17b).** Reaction time: 6 h; temperature 175–180°C; flash chromatography (SiO_2, 3:1 hexanes/EtOAc); total yield of the cycloadducts 93%; R_f 0.33 (1:1 hexanes/EtOAc); mp=162–164°C; $[\alpha]_D^{23}$=+109° (c=1.2, $CHCl_3$); ^{1}H NMR (C_6D_6) δ 7.51–7.25 (5H, arom.), 6.97 (d, J=9.0 Hz, 2H, arom.), 6.82 (d, J=8.9 Hz, 2H, arom.), 4.84 (d, J=7.9 Hz, 1H, H-1), 4.12 (d, J=10.4 Hz, 1H, H-3), 4.04 (t, J=8.1 Hz, 1H, H-6a), 3.96 (dd, J=7.7, 4.8 Hz, 1H, H-7a), 3.74 (s, 3H, OCH_3), 3.61 (d, J=13.8 Hz, 1H, 1/2CH_2SO_2), 3.58 (d, J=13.9 Hz, 1H, 1/2CH_2SO_2), 3.53 (dd, J=8.8, 7.1 Hz, 1H, H-3a), 3.27 (dd, J=9.9, 8.2 Hz, 1H, H-3), 2.50 (1H), 2.01–1.83 (4H), 1.50–1.30 (2H), 1.32 (s, 3H, CH_3), 0.96 (s, 3H, CH_3); ^{13}C NMR (C_6D_6) δ 177.2, 174.9, 166.3, 156.4, 140.2, 131.7, 129.2 (2C), 128.8, 126.8 (2C), 121.1 (2C), 114.5 (2C), 66.0, 65.3, 57.4, 55.5, 53.3, 48.8, 48.8, 48.0, 47.9, 44.5, 43.8, 37.5, 33.0, 26.6, 20.4, 20.2; IR ($CHCl_3$) cm^{-1} 3000 (m), 1710 (s, C=O), 1510 (s), 1380 (w), 1320 (w), 1210 (s); HRMS calcd for $C_{30}H_{33}N_3O_6S$ (M^+) 563.2090, found 563.2073.

3.5.8. [3a*R*-[1(1*R,3a*S**,6a*R**),3aα,6α,7aβ)]]-3*H*-3a,6-Methano-2,1-benzisothiazole, hexahydro-8,8-dimethyl-1-[[octahydro-4,6-dioxo-5-phenyl-2-(4-methoxyphenyl)pyrrolo-[3,4-*c*]pyrrol-1-yl]carbonyl]-2,2-dioxide (18b).** R_f 0.50 (1:1 hexanes/EtOAc); $[\alpha]_D^{23}$=+98° (c=0.82, $CHCl_3$); ^{1}H NMR (C_6D_6) δ 7.26 (d, J=9.04 Hz, 2H, arom.), 7.20–6.80 (7H, arom.), 6.10 (s, 1H, H-1), 4.16 (t, J=9.6 Hz, 1H, H-3), 3.89 (dd, J=9.3, 2.1 Hz, 1H, H-3), 3.38 (d, J=8.3 Hz, 1H, H-6a), 3.31 (s, 3H, OCH_3), 3.22 (1H, H-7a), 3.06 (t, J=8.12 Hz, 1H, H-3a), 2.91 (d, J=13.8 Hz, 1H, 1/2CH_2SO_2), 2.88 (d, J=13.9 Hz, 1H, 1/2CH_2SO_2), 2.00 (1H), 1.81 (1H), 1.41–1.22 (3H), 1.13 (s, 3H, CH_3), 1.12 (1H), 0.76 (1H), 0.48 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$) δ 177.1, 172.0, 170.8, 153.0, 139.9, 131.7, 129.1 (2C), 128.8, 126.4 (2C), 115.6 (2C), 115.0 (2C), 65.1, 63.8, 55.7, 52.9, 52.4, 49.7, 49.1, 48.0, 44.7, 43.2, 38.4, 32.8, 26.4, 21.2, 19.2; IR ($CHCl_3$) cm^{-1} 3000 (m), 1720 (s,

C═O), 1515 (s), 1375 (m), 1335 (m), 1230 (s); HRMS calcd for $C_{30}H_{33}N_3O_6S$ (M^+) 563.2090, found 563.2099.

3.5.9. [3a*R*-[1(1*S,3a*S**,6a*R**),3aα,6α,7aβ)]]-3*H*-3a,6-Methano-2,1-benzisothiazole, hexahydro-8,8-dimethyl-1-[[octahydro-4,6-dioxo-5-phenyl-2-(4-methoxyphenyl)pyrrolo-[3,4-*c*]pyrrol-1-yl]carbonyl]-2,2-dioxide (19b).** R_f 0.31 (1:1 hexanes/EtOAc); mp=162–164°C; $[\alpha]_D^{23}=+109°$ (*c*= 1.2, $CHCl_3$); ^1H NMR (C_6D_6) δ 7.55 (d, *J*=8.2 Hz, 2H, arom.), 7.20–7.05 (3H, arom.), 6.93 (d, *J*=9.0 Hz, 2H, arom.), 6.81 (d, *J*=9.1 Hz, 2H, arom.), 5.26 (d, *J*=9.2 Hz, 1H, H-1), 4.02 (dd, *J*=9.3, 3.5 Hz, 1H, H-3), 3.83 (dd, *J*= 7.7, 4.9 Hz, 1H, H-7a), 3.76 (t, *J*=9.0 Hz, 1H, H-6a), 3.32 (s, 3H, OCH_3), 2.91 (t, *J*=9.2 Hz, 1H, H-3), 2.88 (d, *J*=13.7 Hz, 1H, 1/2CH_2SO_2), 2.85 (d, *J*=13.7 Hz, 1H, 1/2CH_2SO_2), 2.70 (ddd, *J*=9.1, 8.5, 3.5 Hz, 1H, H-3a), 1.93 (1H), 1.73 (dd, *J*=8.0, 6.1 Hz, 1H), 1.40–1.14 (2H), 1.13 (s, 3H, CH_3), 1.08–0.96 (1H), 0.67–0.45 (2H), 0.41 (s, 3H, CH_3); ^{13}C NMR (C_6D_6) δ 176.0, 175.1, 169.5, 154.4, 140.6, 132.9, 128.8 (2C), 128.3, 127.5 (2C), 118.1 (2C), 114.7 (2C), 65.7, 64.7, 54.8, 54.0, 52.5, 48.5, 48.2, 47.3, 44.7, 44.4, 38.4, 32.2, 25.8, 20.9, 19.4; IR ($CHCl_3$) cm^{-1} 3000 (m), 1720 (s, C═O), 1510 (s), 1370 (w), 1335 (w), 1240 (s), 1125 (w), 1040 (s).

3.5.10. [3a*R*-[1(1*R,3a*S**,6a*R**),3aα,6α,7aβ]]-3*H*-3a,6-Methano-2,1-benzisothiazole, 7,7-dichloro-4,5,6,7-tetrahydro-8,8-dimethyl-1-[[octahydro-4,6-dioxo-5-phenyl-2-(phenylmethyl)pyrrolo[3,4-*c*]pyrrol-1-yl]carbonyl]-2,2-dioxide (18c).** Reaction time: 8 h; temperature 184–186°C; flash chromatography (SiO_2, 4:1 hexanes/EtOAc); total yield of the cycloadducts 91%; R_f 0.46 (2:1 hexanes/EtOAc); mp=225–227°C; $[\alpha]_D^{22}=+12°$ (c=0.5, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 7.50–7.20 (10 H, 2×Ph), 5.08 (s, 1H, H-1), 4.55 (s, 1H, H-7a), 4.14 (d, *J*=13.6 Hz, 1H, 1/2CH_2Ph), 3.88 (d, *J*=13.7 Hz, 1H, 1/2CH_2Ph), 3.73 (dd, *J*=9.1, 6.7 Hz, 1H, H-6a), 3.58 (d, *J*=13.8 Hz, 1H, 1/2CH_2SO_2), 3.52 (d, *J*=13.8 Hz, 1H, 1/2CH_2SO_2), 3.38 (dd, *J*=9.0, 6.4 Hz, 1H, H-3), 3.24 (d, *J*=8.67 Hz, 1H, H-3a), 2.60 (d, *J*=4.27 Hz, 1H), 2.45 (1H), 2.01 (3H), 1.62 (1H), 1.52 (s, 3H, CH_3), 1.11 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$) δ 177.7, 175.3, 173.3, 138.4, 132.0, 129.2 (2C), 128.7, 128.5 (2C), 128.0 (2C), 127.2, 126.4 (2C), 94.0, 78.1, 67.5, 62.3, 53.4, 53.3, 52.7, 50.8, 50.3, 49.7, 44.0, 31.6, 25.5, 24.3, 22.9; IR ($CHCl_3$) cm^{-1} 3000 (m), 1715 (s, C═O), 1200 (s), 750 (s); HRMS calcd for $C_{15}H_{18}NO_3$ ($[M-C_{11}H_{14}NO_3SCl_2)]^+$) 305.1289, found 305.1292.

3.5.11. [3a*R*-[1(1*S,3a*S**,6a*R**),3aα,6α,7aβ]]-3*H*-3a,6-Methano-2,1-benzisothiazole, 7,7-dichloro-4,5,6,7-tetrahydro-8,8-dimethyl-1-[[octahydro-4,6-dioxo-5-phenyl-2-(phenylmethyl)pyrrolo[3,4-*c*]pyrrol-1-yl]carbonyl]-2,2-dioxide (19c).** R_f 0.21 (2:1 hexanes/EtOAc); $[\alpha]_D^{22}=-22°$ (c=1.9, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 7.50–7.23 (10 H, 2×Ph), 4.57 (s, 1H, H-7a), 4.22 (d, *J*=8.5 Hz, 1H, H-1), 4.10 (d, *J*=13.3 Hz, 1H, 1/2CH_2Ph), 3.97 (t, *J*=8.4 Hz 1H, H-6a), 3.59 (s, 2H, CH_2SO_2), 3.51 (d, *J*=13.3 Hz, 1H, 1/2CH_2Ph), 3.47 (d, *J*=10.7 Hz, 1H, H-3), 3.32 (t, *J*=7.3 Hz, 1H, H-3a), 2.63 (dd, *J*=9.6, 7.3 Hz 1H, H-3), 2.58 (d, *J*=4.4 Hz 1H), 2.45 (1H), 2.00 (2H), 1.62 (1H), 1.55 (s, 3H, CH_3), 1.12 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$) δ 177.3, 175.7, 169.9, 135.8, 132.1, 129.4,(2C), 129.1 (2C), 128.6, 128.4 (2C), 127.6, 126.8 (2C), 93.6, 79.5, 68.6, 62.4, 55.9, 53.4, 52.8, 50.8, 49.4, 48.1, 44.5, 31.8, 25.3, 24.7, 23.0; IR ($CHCl_3$) cm^{-1} 3000 (m), 1710 (s, C═O), 1490 (w), 1380 (m), 1340 (m), (1200 (s); HRMS calcd for $C_{15}H_{18}NO_3$ ($[M-C_{11}H_{14}NO_3SCl_2]^+$) 305.1289, found 305.1298.

3.5.12. [3a*R*-[1(2*R,3*R**),3aα,6α,7aβ)]]-3-Pyrrolidinedicarboxylic acid, 1-(phenylmethyl)-2-[(tetrahydro-8,8-dimethyl-3*H*-3a,6-methano-2,1-benzisothiazol-1(4*H*)-yl)-carbonyl]-methyl ester, *S*,*S*-dioxide (22a).** Reaction time: 20 h; temperature 195–197°C; flash chromatography (SiO_2, 2:1 hexanes/EtOAc, all the diastereomers eluted together but most of **22a** was separated by recrystallization from 3:1 hexanes/EtOAc); total yield of the cycloadducts 75.0%; R_f 0.59 (2:1 hexanes/EtOAc); mp=151–152°C; $[\alpha]_D^{23}=+156°$ (*c*=2.0, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 7.38–7.20 (5H, Ph), 4.26 (d, *J*=5.7 Hz, 1H, H-2), 3.93 (1H, H-7a), 3.92 (d, *J*=12.9 Hz, 1H, 1/2CH_2Ph), 3.68 (s, 3H, OCH_3), 3.56 (d, *J*=13.1 Hz, 1H, 1/2CH_2Ph), 3.51 (d, *J*=13.7 Hz, 1H, 1/2CH_2SO_2), 3.42 (d, *J*=13.7 Hz, 1H, 1/2CH_2SO_2), 3.08 (1H, H-3), 3.02 (1H, H-5), 2.60 (q, *J*=8.5 Hz, 1H, H-5), 2.08 (4H), 1.89 (3H), 1.42–1.25 (2H), 1.15 (s, 3H, CH_3), 0.97 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$) δ 173.8, 172.7, 139.1, 128.8 (2C), 128.2 (2C), 127.0, 68.9, 65.4, 57.6, 53.3, 52.2, 51.9, 48.8, 48.5, 47.8, 44.7, 38.4, 33.0, 28.2, 26.5, 20.8, 20.0; IR ($CHCl_3$) cm^{-1} 3010 (m), 1735 (s), 1700 (s), 1450 (w), 1335 (m), 1265 (m), 1200 (m), 1130 (m); HRMS calcd for $C_{24}H_{33}N_2O_5S$ ($[M+H]^+$) 461.2110, found 461.2105.

3.5.13. 3-Pyrrolidinedicarboxylic acid, 1-(phenylmethyl)-5-[(tetrahydro-8,8-dimethyl-3*H*-3a,6-methano-2,1-benzisothiazol-1(4*H*)-yl)carbonyl]-methyl ester, *S*,*S*-dioxide (23a). Separation of this diastereomer from other minor diastereomers was accomplished by HPLC (100 mg sample, 3:1 hexanes/EtOAc, semiprep column, rt, 10 mL/min, Schimadzu-spectroflow detector) R_f 0.58 (2:1 hexanes/EtOAc); mp=142–144°C; $[\alpha]_D^{23}=+130°$ (*c*=1.9, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 7.38–7.20 (5H, Ph), 4.10 (dd, *J*= 9.40, 6.2 Hz, 1H, H-2), 3.92 (1H, H-7a), 3.91 (d, *J*= 12.7 Hz, 1H, 1/2CH_2Ph), 3.65 (s, 3H, OCH_3), 3.51 (d, *J*= 13.8 Hz, 1H, 1/2CH_2SO_2), 3.47 (d, *J*=12.9 Hz, 1H, 1/ 2CH_2Ph), 3.44 (d, *J*=13.8 Hz, 1H, 1/2CH_2SO_2), 3.23 (t, *J*=8.5 Hz, 1H, H-5), 3.11 (1H, H-4), 2.68 (ddd, *J*=9.5, 7.6, 5.8 Hz, 1H, H-3), 2.60 (t, *J*=8.6 Hz, 1H, H-5), 2.08 (3H), 1.88 (3H), 1.40 (2H), 1.13 (s, 3H, CH_3), 0.93 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$) δ 174.0, 172.4, 138.2, 129.1 (2C), 128.3 (2C), 127.2, 65.6, 65.2, 57.6, 55.0, 53.2, 52.0, 48.7, 47.9, 44.6, 41.3, 38.3, 33.4, 32.8, 26.5, 20.9, 19.9; IR ($CHCl_3$) cm^{-1} 2970 (m), 1730 (s), 1700 (s), 1450 (w), 1330 (s), 1260 (s), 1210 (s), 1130 (s); HRMS *m*/*z* calcd for $C_{13}H_{16}NO_2$ ($[M-C_{11}H_{16}NO_3S]^+$) 218.1181, found 218.1186.

3.5.14. [3a*R*-[1(2*R,3*R**),3aα,6α,7aβ)]]-3-Pyrrolidinedicarboxylic acid, 1-(phenylmethyl)-2-[(7,7-dichloro-4,5,6,7-tetrahydro-8,8-dimethyl-3*H*-3a,6-methano-2,1-benzisothiazol-1(4*H*)-yl)carbonyl]-methyl ester, *S*,*S*-dioxide (22c).** Reaction time: 9 h; temperature 184–186°C; flash chromatography (SiO_2, 3:1 hexanes/EtOAc, this diastereomer was separated from the other one via partial recrystallization from 1:1 hexanes/EtOAc; total yield of the cycloadducts 84%; R_f 0.45 (2:1 hexanes/

EtOAc); mp=201–203°C; $[\alpha]_D^{22}=+27°$ (c=0.74, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 7.40–7.20 (5H, Ph), 4.55 (s, 1H, H-7a), 4.51 (d, J=4.8 Hz, 1H, H-2), 4.02 (d, J=13.3 Hz, 1H, 1/2CH_2Ph), 3.70 (s, 3H, OCH_3), 3.65 (d, J=13.3 Hz, 1H, 1/2CH_2Ph), 3.52 (d, J=13.7 Hz, 1H, 1/2CH_2SO_2), 3.46 (d, J=13.8 Hz, 1H, 1/2CH_2SO_2), 3.32 (1H, H-3), 3.03 (1H, H-5), 2.65 (dd, J=15.9, 8.6, 1H, H-5), 2.57 (d, J=4.4 Hz, 1H), 2.45 (1H), 2.20–1.90 (4H), 1.62 (2H), 1.48 (s, 3H, CH_3), 1.09 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$) δ 174.5, 170.0, 139.2, 128.7 (2C), 122.2, 126.9 (2C), 93.7, 78.5, 69.6, 62.3, 57.1, 52.9, 52.2, 51.4, 50.6, 49.6, 48.6, 31.6, 28.6, 25.4, 23.8, 22.9; IR ($CHCl_3$) cm^{-1} 3010 (m), 1730 (s, C=O), 1430 (w), 1340 (s), 1265 (m), (1215 (s), 1130 (m); HRMS calcd for $C_{13}H_{16}NO_2$ ($[M-C_{11}H_{14}NO_3SCl_2]^+$) 218.1181, found 218.1181.

3.5.15. 3-Pyrrolidinedicarboxylic acid, 1-(phenylmethyl)-5-[(7,7-dichloro-4,5,6,7-tetrahydro-8,8-dimethyl-3*H*-3a,6-methano-2,1-benzisothiazol-1(4*H*)-yl)carbonyl]-methyl ester, *S*,*S*-dioxide (23c). R_f 0.46 (2:1 hexanes/EtOAc); mp=51–53°C; $[\alpha]_D^{22}=+82°$ (c=0.88, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 7.40–7.20 (5H, Ph), 4.53 (s, 1H, H-7a), 4.33 (d, J=9.3, 5.5 Hz, 1H, H-2), 4.02 (d, J=13.2 Hz, 1H, 1/2CH_2Ph), 3.64 (s, 3H, OCH_3), 3.58 (d, J=12.9 Hz, 1H, 1/2CH_2Ph), 3.53 (d, J=13.7 Hz, 1H, 1/2CH_2SO_2), 3.49 (d, J=13.8 Hz, 1H, 1/2CH_2SO_2), 3.26 (t, J=8.3 Hz, 1H, H-5), 3.16 (1H, H-4), 2.68 (2H), 2.57 (d, J=4.40 Hz, 1H), 2.45 (2H), 2.00 (2H), 1.62 (2H), 1.47 (s, 3H, CH_3), 1.09 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$) δ 174.3, 174.2; 138.5 128.8 (2C), 128.2, 127.1 (2C), 93.7, 78.4, 66.4, 62.2, 57.1, 54.6, 52.8, 52.0, 50.7, 49.6, 41.2, 33.5, 31.6, 25.4, 24.1, 22.9; IR ($CHCl_3$) cm^{-1} 3010 (m), 1730 (s), 1430 (w), 1340 (s), 1265 (m), (1215 (s), 1130 (m); HRMS calcd for $C_{13}H_{16}NO_2$ ($[M-C_{11}H_{14}NO_3SCl_2]^+$) 218.1181, found 218.1177.

3.5.16. [3a*R*-[(3a*R,4*R**,6a*S**),3aα,6α,7aβ)]]-3*H*-3a,6-Methano-2,1-benzisothiazole, hexahydro-8,8-dimethyl-4-[[tetrahydro-1,3-dioxolo-5-(phenylmethyl)-2-oxo-[4,5-*c*]pyrrole-4-yl]carbonyl]-2,2-dioxide (26a).** R_f=0.16 (2:1 hexanes/EtOAc); $[\alpha]_D^{23}=-5.8°$ (c=1.7, $CHCl_3$); mp=101–103°C; ^1H NMR ($CDCl_3$ δ 7.38–7.26 (5H, Ph), 5.49 (dd, J=7.1, 5.4 Hz, 1H, H-3a), 4.98 (dd, J=7.1, 4.2 Hz, 1H, H-6a), 4.05 (dd, J=7.2, 5.5 Hz, 1H, H-7a), 3.97 (d, J=5.4 Hz, 1H, H-4), 3.87 (d, J=13.3 Hz, 1H, 1/2CH_2Ph), 3.54 (d, J=13.8 Hz, 1H, 1/2CH_2SO_2), 3.49 (d, J=13.3 Hz, 1H, 1/2CH_2Ph), 3.47 (d, J=13.8 Hz, 1H, 1/2CH_2SO_2), 3.32 (d, J=11.7 Hz, 1H, H-6), 2.50 (dd, J=11.7, 4.5 Hz, 1H, H-6), 2.13 (1H), 1.89 (3H), 1.48–1.22 (3H), 1.18 (s, 3H, CH_3), 0.99 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$) δ 164.6, 154.2, 135.8, 129.1 (2C), 128.4 (2C), 127.7, 79.1, 78.0, 68.6, 66.0, 56.1, 55.7, 53.3, 48.9, 47.9, 44.8, 38.8, 33.0, 26.4, 21.2, 19.9; IR ($CHCl_3$) cm^{-1} 3670 (w), 3000 (m), 1820 (s), 1710 (s, C=O), 1330 (m), 1200 (s), 1150 (m), 1080 (m); HRMS calcd for $C_{12}H_{12}NO_3$ ($[M-C_{11}H_{16}NO_3S]^+$) 218.0817, found 218.0821.

3.5.17. [3a*R*-[(3a*S,4*S**,6a*R**),3aα,6α,7aβ)]]-3*H*-3a,6-Methano-2,1-benzisothiazole, hexahydro-8,8-dimethyl-4-[[tetrahydro-1,3-dioxolo-5-(phenylmethyl)-2-oxo-[4,5-*c*]pyrrole-4-yl]carbonyl]-2,2-dioxide (27a).** Reaction time: 15 h; temperature 195–197°C; flash chromatography (SiO_2, 3:1 hexanes/EtOAc); total yield of the cycloadducts 51% (pyrrole **17a** was formed in 22%); R_f=0.20 (2:1 hexanes/EtOAc); $[\alpha]_D^{23}=+149°$ (c=2.0, $CHCl_3$); ^1H NMR ($CDCl_3$ δ 7.35–7.26 (5H, Ph), 5.47 (dd, J=7.0, 5.1 Hz, 1H, H-3a), 4.97 (dd, J=7.0, 4.3 Hz, 1H, H-6a), 4.11 (d, J=13.2 Hz, 1H, 1/2CH_2Ph), 4.00 (dd, J=7.7, 4.8 Hz, 1H, H-7a), 3.88 (d, J=5.1 Hz, 1H, H-4), 3.55 (d, J=13.7 Hz, 1H, 1/2CH_2SO_2), 3.49 (d, J=13.7 Hz, 1H, 1/2CH_2SO_2), 3.40 (d, J=13.3 Hz, 1H, 1/2CH_2Ph), 3.27 (d, J=11.7 Hz, 1H, H-6), 2.38 (dd, J=11.8, 4.4 Hz, 1H, H-6), 2.28–1.86 (4H), 1.89 (3H), 1.49–1.20 (3H), 1.18 (s, 3H, CH_3), 0.98 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$) δ 164.64, 154.1, 135.9, 129.1 (2C), 128.2 (2C), 127.6, 80.1, 77.8, 69.6, 65.5, 56.2, 55.8, 53.3, 49.1, 48.0, 44.4, 37.9, 32.7, 26.6, 20.4, 20.0; IR ($CHCl_3$) cm^{-1} 3000 (m), 1810 (s), 1710 (m), 1330 (m), 1260 (m), 1210 (m), 1150 (m), 1080 (m); HRMS calcd for $C_{12}H_{12}NO_3$ ($[M-C_{11}H_{16}NO_3S]^+$) 218.0817, found 218.0805.

3.5.18. [3a*R*-[(3a*R,4R*,6a*S**),3aα,6α,7aβ)]]-3*H*-3a,6-Methano-2,1-benzisothiazole, hexahydro-8,8-dimethyl-4-[[tetrahydro-1,3-dioxolo-5-(4-methoxyphenyl)-2-oxo-[4,5-*c*]pyrrole-4-yl]carbonyl]-2,2-dioxide (26b).** R_f 0.40 (1:1 hexanes/EtOAc); mp=322–324°C; $[\alpha]_D^{23}=-32°$ (c=1.4, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 6.82 (d, J=9.2 Hz, 2H, arom.), 6.76 (d, J=9.2 Hz, 2H, arom.), 5.61 (dd, J=7.4, 6.7 Hz, 1H, H-3a), 5.25 (dt, J=5.8, 2.3 Hz, 1H, H-6a), 5.06 (d, J=6.7 Hz, 1H, H-4), 4.03 (dd, J=11.4, 2.0 Hz, 1H, H-6), 3.96 (dd, J=7.6, 4.9 Hz, 1H, H-7a), 3.74 (s, 3H, OCH_3), 3.60 (d, J=13.8 Hz, 1H, 1/2CH_2SO_2), 3.55 (dd, J=11.3, 5.9 Hz, 1H, H-6), 3.53 (d, J=13.9 Hz, 1H, 1/2CH_2SO_2), 2.20–1.85 (5H), 1.48–1.28 (2H), 1.24 (s, 3H, CH_3), 0.99 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$) δ 167.3, 154.0, 153.5, 139.0, 115.8 (2C), 114.9 (2C), 78.6, 78.0, 65.7, 64.5, 55.7, 55.2, 53.2, 49.1, 47.9, 44.9, 38.3, 32.9, 26.2, 20.9, 20.0; IR ($CHCl_3$) cm^{-1} 3680 (w), 3010 (m), 2950 (w), 2480 (w), 1735 (s, C=O), 1695 (m), 1510 (s), 1430 (m), 1330 (s), 1260 (s), (1215 (s), 1125 (m), 1030 (m); HRMS calcd for $C_{23}H_{28}N_2O_7S$ (M^+) 476.1617, found 476.1624.

3.5.19. [3a*R*-[(3a*S,4*S**,6a*R**),3aα,6α,7aβ)]]-3*H*-3a,6-Methano-2,1-benzisothiazole, hexahydro-8,8-dimethyl-4-[[tetrahydro-1,3-dioxolo-5-(4-methoxyphenyl)-2-oxo-[4,5-*c*]pyrrole-4-yl]carbonyl]-2,2-dioxide (27b).** Reaction time: 5 h; temperature 188–190°C; flash chromatography (SiO_2, 2:1 hexanes/EtOAc); total yield of the cycloadducts 83%; R_f 0.30 (1:1 hexanes/EtOAc); mp=139–140°C; $[\alpha]_D^{23}=+38°$ (c=1.0, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 6.79 (d, J=9.2 Hz, 2H, arom.), 6.71 (d, J=9.2 Hz, 2H, arom.), 5.55 (t, J= 7.5 Hz, 1H, H-3a), 5.30 (d, J=7.2 Hz, 1H, H-4), 5.26 (1H, H-6a), 3.96 (dd, J=7.9, 5.9 Hz, 1H, H-7a), 3.97 (d, J=11.0 Hz, 1H, H-6), 3.76 (dd, J=10.9, 6.6 Hz, 1H, H-6), 3.74 (s, 3H, OCH_3), 3.60 (d, J=13.8 Hz, 1H, 1/2CH_2SO_2), 3.53(d, J=13.9 Hz, 1H, 1/2CH_2SO_2), 1.98–1.75 (4H), 1.47–1.28 (3H), 1.21 (s, 3H, CH_3), 0.99 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$) δ 167.3, 153.8, 153.5, 139.1, 115.8 (2C), 114.9 (2C), 78.5, 78.1, 65.7, 64.6, 55.7, 55.2, 53.2, 49.1, 47.9, 44.9, 38.2, 32.9, 26.2, 20.9, 19.9; IR ($CHCl_3$) cm^{-1} 3000 (m), 2640 (m), 1810 (s), 1700 (m), 1510 (s), 1330 (s), 1225 (s), 1150 (m), 1090 (s); HRMS calcd for $C_{23}H_{28}N_2O_7S$ (M^+) 476.1617, found 476.1616.

3.5.20. [3a*R*-[(3a*S,4*R**,6a*R**),3aα,6α,7aβ)]]-3*H*-3a,6-Methano-2,1-benzisothiazole, hexahydro-8,8-dimethyl-4-[[tetrahydro-1,3-dioxolo-5-(4-methoxyphenyl)-2-oxo-**

[4,5-*c*]pyrrole-4-yl]carbonyl]-2,2-dioxide (28b). R_f 0.19 (1:1 hexanes/EtOAc); mp=139–140°C; $[\alpha]_D^{26}$=+39° (*c*=1.3, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 6.77 (s, 4H, arom.), 5.48 (s, 1H, H-4), 5.34 (dd, *J*=7.1, 4.8 Hz, 1H, H-6a), 5.25 (d, *J*=7.1 Hz, 1H, H-3a), 3.96 (dd, *J*=11.4, 5.0 Hz, 1H, H-6), 3.83 (d, *J*=11.4 Hz, 1H, H-6), 3.82 (dd, *J*=7.3, 5.0 Hz, 1H, H-7a), 3.74 (s, 3H, OCH_3), 3.59 (d, *J*=13.8 Hz, 1H, 1/2CH_2SO_2), 3.48 (d, *J*=13.8 Hz, 1H, 1/2CH_2SO_2), 1.98–1.62 (4H), 1.42–1.12 (3H), 1.07 (s, 3H, CH_3), 0.96 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$) δ 170.0, 153.9, 153.6, 138.9, 116.1 (2C), 114.9 (2C), 81.3, 79.2, 66.8, 65.1, 55.7, 55.6, 55.3, 53.1, 49.4, 47.9, 44.6, 44.5, 38.1, 32.9, 26.4, 20.6, 19.9, 19.9; IR ($CHCl_3$) cm^{-1} 3000 (m), 2960 (m), 1810 (s), 1680 (m), 1510 (s), 1330 (s), 1240 (s), 1160 (s), 1050 (s).

3.5.21. [3a*R*-[(3a*S,4*S**,6a*R**),3aα,6α,7aβ)]]-3*H*-3a,6-Methano-2,1-benzisothiazole, 7,7-dichloro-4,5,6,7-tetrahydro-8,8-dimethyl-4-[[tetrahydro-1,3-dioxolo-5-(phenylmethyl)-2-oxo-[4,5-*c*]pyrrole-4-yl]carbonyl]-2,2-dioxide (27c).** Reaction time: 15 h; temperature 167–169°C; flash chromatography (SiO_2, 8:1 $CHCl_3$/EtOAc); total yield of the cycloadducts 52% (pyrrole **30c** was formed in 12%); R_f 0.28 (5:1 $CHCl_3$/EtOAc); mp=252–253°C; $[\alpha]_D^{22}$=−61° (*c*=, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 7.38–7.25 (5H, Ph), 5.50 (dd, *J*=7.0, 5.4 Hz, 1H, H-3a), 4.98 (dd, *J*=7.0, 4.2 Hz, 1H, H-6a), 4.62 (s, 1H, H-7a), 4.10 (d, *J*=13.3 Hz, 1H, 1/2CH_2Ph), 3.98 (d, *J*=5.3 Hz, 1H, H-4), 3.58 (s, 2H, CH_2SO_2), 3.52 (d, *J*=13.3 Hz, 1H, 1/2CH_2Ph), 3.31 (d, *J*=11.6 Hz, 1H, H-6), 2.59 (d, *J*=4.4 Hz, 1H), 2.49 (2H), 2.12–1.94 (2H), 1.63 (1H), 1.53 (s, 3H, CH_3), 1.12 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$) δ 166.5, 154.1, 135.4, 129.4 (2C), 128.5 (2C), 127.8, 93.3, 79.3, 78.0, 69.0, 62.3, 55.6, 55.1, 52.9, 50.9, 49.5, 31.8, 25.4, 24.5, 22.9; IR ($CHCl_3$) cm^{-1} 2950 (w), 1810 (s), 1720 (m), 1330 (m), 1190 (m), 1130 (m), 900 (m); HRMS calcd for $C_{12}H_{12}NO_3$ ([M−$C_{11}H_{14}NO_3SCl_2$]$^+$) 218.0817, found 218.0821.

3.5.22. [3a*R*-[(3a*S,4*R**,6a*R**),3aα,6α,7aβ)]]-3*H*-3a,6-Methano-2,1-benzisothiazole, 7,7-dichloro-4,5,6,7-tetrahydro-8,8-dimethyl-4-[[tetrahydro-1,3-dioxolo-5-(phenylmethyl)-2-oxo-[4,5-*c*]pyrrole-4-yl]carbonyl]-2,2-dioxide (28c).** R_f 0.8, 7:1 ($CHCl_3$/EtOAc); $[\alpha]_D^{22}$=+10° (*c*=0.5, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 7.40–7.20 (5H, Ph), 5.50 (d, *J*=6.8 Hz, 1H, H-3a), 5.12 (dd, *J*=6.7, 4.6 Hz, 1H, H-6a), 4.86 (s, 1H, H-4), 4.49 (s, 1H, H-7a), 4.16 (d, *J*=13.3 Hz, 1H, 1/2CH_2Ph), 3.93 (d, *J*=13.3 Hz, 1H, 1/2CH_2Ph), 3.58 (d, *J*= 13.7 Hz, 1H, 1/2CH_2SO_2), 3.52 (d, *J*=13.7 Hz, 1H, 1/2CH_2SO_2), 3.50 (dd, *J*=11.5, 6.54 Hz, 1H, H-6), 3.18 (d, *J*=11.6 Hz, 1H, H-6), 2.60 (d, *J*=4.52 Hz, 1H), 2.55–2.35 (1H), 2.12–1.90 (2H), 1.62 (1H), 1.47 (s, 3H, CH_3), 1.12 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$) δ 170.9, 154.2, 137.7, 128.6 (2C), 128.2 (2C), 127.4, 93.7, 82.4, 79.6, 78.1, 70.2, 62.1, 55.6, 52.9, 52.6, 51.0, 49.7, 31.6, 25.4, 24.2, 22.9; IR ($CHCl_3$) cm^{-1} 3000 (m), 1810 (s), 1715 (m), 1200 (s), 1145 (m); HRMS calcd for $C_{12}H_{12}NO_3$ ([M−$C_{11}H_{14}NO_3SCl_2$]$^+$) 218.0817, found 218.0811.

3.5.23. L-*trans*-2,3-Pyrrolidinedicarboxylic acid (24). A solution of **22a** (130 mg, 0.28 mmol) in MeOH (2 mL) was treated with 10% Pd–C (130 mg), at room temperature, under an H_2 atmosphere. The reaction mixture was stirred at this temperature until judged complete by TLC (usually 2 h), filtered through a pad of Celite, and the filtrate concentrated to give crude debenzylated product in quantitative yield. This crude product was added to a stirring solution of 2 equiv. BnSH and 1.5 equiv. *n*-BuLi (2.5 M in hexanes) at 0°C in THF (concentration approx. 0.2 M). After confirming by the TLC that the starting material was consumed, the reaction mixture was diluted with ether and quenched with 6.0N HCl. The organic phase was separated and the aqueous layer was extracted with 3×EtOAc. The combined organic layers were dried ($MgSO_4$), concentrated in vacuo and the residue was purified by flash chromatography on silica gel to give the sultam auxiliary in 80% yield. After freeze-drying the aqueous layer, the resulting solids were dissolved in a minimum amount of water and loaded onto an anion-exchange column containing 2 g (wet weight) Bio Rad Ag-1-X2 anion-exchange resin. The column was washed with five bed volumes of water, and the crude product was eluted with 1% aqueous acetic acid. The ninhydrin (Char B) active fractions were collected and freeze-dried to give 24 in 72% yield; mp=330–332°C; $[\alpha]_D^{25}$=−32° (*c*=0.3, H_2O) [lit.[17] mp=333–335°C, $[\alpha]_D^{26}$=−34.3° (*c*=0.28, H_2O)]; ^1H NMR (D_2O) δ 4.27 (d, *J*=5.37 Hz, 1H, H-2), 3.26 (1H), 3.13 (1H), 2.20–2.00 (2H)-these data matched those of an authentic sample; HRMS (FAB/glycerol) calcd for $C_5H_8NO_2$ ([M−CO_2H]$^+$) 114.0555, found 114.0556.

3.5.24. 1,4-Dideoxy-1,4-imino-D-lyxitol hydrochloride (ent-31). Debenzylation and auxiliary cleavage were carried out as described above for compound **22a.** The solids obtained from the aqueous layer after freeze-drying were dissolved in a minimum of water and loaded onto an ion-exchange column containing 2 g (wet weight) of Amberlite-IR-120 (H^+ form). The column was eluted with aqueous ammonia and the ninhydrin (char B) active fractions were concentrated in vacuo, acidified to pH 4 with dilute HCl solution, and freeze-dried to afford 28 mg (65%) of **ent-31**; mp= 158–160°C; $[\alpha]_D^{24}$=+24° (*c*=0.9, H_2O) [lit.[19] mp=157–159°C, $[\alpha]_D^{20}$=+18.8° (*c*=0.16, H_2O)]; ^1H NMR (D_2O) δ 4.28 (ddd, *J*=7.3, 6.3, 4.2 Hz, 1H, H-2), 4.29 (t, *J*= 4.1 Hz, 1H, H-3), 3,78 (dd, *J*=5.0, 4.9 Hz, 1H, H-4), 3.68 (dd, *J*=8.32, 12.1 Hz, 1H, H-5), 3.54 (1H, H-5′), 3.33 (dd, *J*=7.61, 7.35 Hz, 1H, H-1), 3.09 (dd, *J*=7.38, 7.33 Hz, 1H, H-1′); HRMS calcd for $C_4H_7NO_2S$ ([M−$HClCH_2OH$]$^+$) 102.0555, found 102.0551. The sultam auxiliary was recovered in 77% yield.

3.5.25. 1,4-Dideoxy-1,4-imino-L-lyxitol hydrochloride (31). Following the same procedure as above, **33** was isolated in 67% yield; mp=160–162°C; $[\alpha]_D^{24}$=−21° (*c*=0.5, H_2O) [lit.[3g] mp=162–163°C, $[\alpha]_D^{29}$=−20.3° (*c*=0.28, H_2O)]; The ^1H NMR spectrum (D_2O) was same as **ent-33**; HRMS calcd for $C_4H_7NO_2S$ ([M−$HClCH_2OH$]$^+$) 102.0555, found 102.0549. The recovered sultam auxiliary was obtained in 72% yield.

3.6. General procedure for amine condensation

A mixture of **10**, benzaldehyde (1.5 equiv.), and 4 Å molecular sieves (ca. 1 g) in toluene (concentration approx. 0.3 M) was stirred at 80–85°C for 10 min at which time a solution of dipolarophile (3 equiv.) in toluene was added. The resulting mixture was stirred at this temperature until

TLC analysis indicated complete consumption of **10**. The reaction mixture was filtered through a pad of Celite, concentrated, and purified by flash chromatography on silica gel.

3.6.1. [2*S*-[2α,3α,4α,5α(3a*S,6*R**,7a*R**)]]-3,4-Pyrrolidinedicarboxylic acid, 2-phenyl-5-[(tetrahydro-8,8-dimethyl-3*H*-3a,6-methano-2,1-benzisothiazol-1(4*H*)-yl)carbonyl]-dimethyl ester, *S*,*S*-dioxide (37).** Flash chromatography (SiO_2, 2:1 hexanes/EtOAc, further purification was accomplished by PTLC on silica gel, eluting three times with 3:1 hexanes/EtOAc); total yield of the cycloadducts 66%; R_f=0.4 (1:1 hexanes/EtOAc); $[\alpha]_D^{22}$=+39° (*c*=0.62, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 7.4–7.2 (5H, Ph), 4.55 (dd, *J*=8.6, 3.2 Hz, 1H, H-2), 4.44 (dd, *J*=7.3, 5.9 Hz, 1H, H-5), 4.01 (t, *J*=8.9 Hz, 1H, H-3), 4.00 (dd, *J*=5.01, 2.9 Hz, 1H, H-7a), 3.76 (dd, *J*=7.5, 1.7 Hz, 1H, H-4), 3.56 (s, 3H, OCH_3), 3.49 (s, 2H, CH_2SO_2), 3.18 (s, 3H, OCH_3), 2.48–2.38 (1H), 2.12 (dd, *J*=8.03, 5.90 Hz, 1H), 1.90 (3H), 1.50–1.35 (2H), 1.13 (s, 3H, CH_3), 0.97 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$) δ 170.9, 170.7, 167.6, 136.9, 128.1 (2C), 127.5, 126.8 (2C), 65.7, 64.5, 62.6, 54.2, 53.0, 51.9, 51.9, 51.3, 48.5, 47.8, 44.6, 37.3, 32.9, 26.6, 20.1 (2C); IR ($CHCl_3$) cm^{-1} 3680 (w), 3015 (m), 2960 (w), 2380 (w), 1740 (s), 1325 (m), 1260 (m), (1210 (s), 1125 (m), 1050 (w); HRMS calcd for $C_{25}H_{32}N_2O_7S$ (M^+) 504.1930, found 504.1907.

3.6.2. [2*R*-[2β,3β,4β,5β(3a*S,6*R**,7a*R**)]]-3,4-Pyrrolidinedicarboxylic acid, 2-phenyl-5-[(tetrahydro-8,8-dimethyl-3*H*-3a,6-methano-2,1-benzisothiazol-1(4*H*)-yl)carbonyl]-dimethyl ester, *S*,*S*-dioxide (38).** R_f 0.5 (1:1 hexanes/EtOAc); $[\alpha]_D^{23}$=+1.6° (*c*=1.4, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 7.35–7.20 (5H, Ph), 5.15 (d, *J*=7.7 Hz, 1H, H-2), 4.61 (d, *J*=5.8 Hz, 1H, H-5), 4.23 (t, *J*=7.5 Hz, 1H, H-3), 4.00 (dd, *J*=7.8, 4.9 Hz, H-7a), 3.67 (s, 3H, OCH_3), 3.62 (dd, *J*=7.3, 5.8 Hz, H-4), 3.53 (d, *J*=13.8 Hz, 1H, 1/2CH_2SO_2), 3.46 (d, *J*=13.7 Hz, 1H, 1/2CH_2SO_2), 3.29 (s, 3H, OCH_3), 3.10 (br s, 1H, NH), 1.28–1.18 (1H), 2.10–2.02 (1H), 1.91 (2H), 1.50–1.20 (3H), 1.17 (s, 3H, CH_3), 0.96 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$) δ 171.8, 171.1, 171.0, 137.2, 128.3 (2C), 127.8, 126.3 (2C), 65.3, 65.0, 61.5, 53.47, 52.9, 52.2, 51.3, 49.1, 48.8, 47.8, 44.61, 38.1, 32.7, 26.4, 20.8, 19.9; IR ($CHCl_3$) cm^{-1} 3670 (w), 3010 (m), 2945 (w), 2380 (w), 1730 (s), 1680 (m), 1430 (m), 1330 (s), 1270 (m), (1210 (s), 1130 (m).

3.6.3. [1*R*-[1α(3a*R,6*S**,7a*S**),3α,3aβ,6aβ]]-3*H*-3a,6-Methano-2,1-benzisothiazole, hexahydro-8,8-dimethyl-1-[(hexahydro-4,6-dioxo-3,5-diphenylpyrrolo[3,4-*c*]pyrrol-1-yl)carbonyl]-2,2-dioxide (39a).** Flash chromatography (SiO_2, 2:1 hexanes/EtOAc); total yield of the cycloadducts 84%; R_f 0.5 (1:1 hexanes/EtOAc); mp=270–271°C; $[\alpha]_D^{23}$=+23.7° (*c*=2.42, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 7.46–7.13 (10H, Ph), 4.66 (2H, H-1 and H-3), 4.02 (2H, H-7a and H-6a), 3.62 (t, *J*=8.3 Hz, 1H, H-3a), 3.60 (d, *J*=15.4 Hz, 1H, 1/2CH_2SO_2), 3.55 (d, *J*=15.0 Hz, 1H, 1/2CH_2SO_2), 2.62 (2H), 2.04 (dd, *J*=7.9, 6.0 Hz, 1H), 1.93 (3H), 1.49–1.33 (2H), 1.32 (s, 3H, CH_3), 0.99 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$) δ 174.7, 173.7, 167.6, 136.7, 131.7, 128.9 (2C), 128.4 (2C), 128.3 (2C), 127.0 (2C), 126.3 (2C), 65.7, 63.9, 62.9, 53.2, 50.0, 49.3, 48.76, 47.9, 44.5, 37.2, 32.7, 26.6, 20.3, 20.0; IR ($CHCl_3$) cm^{-1} 3680 (w), 3000 (m), 2950 (w), 1710 (s, C═O), 1495 (m), 1380 (m), 1325 (m), 1260 (m), 1210 (s), 1130 (m); HRMS calcd for $C_{18}H_{15}N_2O_2$ ([M−$C_{11}H_{16}NO_3S$]$^+$) 291.1133 found 291.1114.

3.6.4. [1*R*-[1β(3a*R,6*S**,7a*S**),3β,3aα,6aα]]-3*H*-3a,6-Methano-2,1-benzisothiazole, hexahydro-8,8-dimethyl-1-[(hexahydro-4,6-dioxo-3,5-diphenylpyrrolo[3,4-*c*]pyrrol-1-yl)carbonyl]-2,2-dioxide (40a).** R_f 0.48 (1:1 hexanes/EtOAc); $[\alpha]_D^{23}$=+131° (*c*=0.80, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 7.40–7.18 (10 H, 2×Ph), 4.72 (1H, H-3), 4.66 (m,1H, H-1), 4.23 (t, *J*=7.8 Hz, 1H, H-6a), 4.10 (dd, *J*=8.0, 5.0 Hz, 1H, H-7a), 3.65 (t, *J*=8.2 Hz, 1H, H-3a), 3.56 (s, 2H, CH_2SO_2), 2.83 (br s, 1H, NH), 2.33 (1H), 2.18 (dd, *J*=7.83, 6.32 Hz, 1H), 1.91 (3H), 1.51–1.24 (2H), 1.20 (s, 3H, CH_3), 1.01 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$) δ 174.9, 173.7, 168.4, 136.0, 131.7, 128.9 (2C), 128.4 (2C), 128.2 (2C), 126.9 (2C), 126.3 (2C), 66.1, 65.2, 62.9, 53.0, 50.9, 50.3, 48.9, 47.9, 44.8, 38.5, 32.8, 26.2, 21.0, 19.9; IR ($CHCl_3$) cm^{-1} 3680 (w), 3010 (m), 2960 (w), 2380 (w), 1710 (s, C═O), 1495 (m), 1375 (m), 1330 (m), 1210 (s), 1130 (m); HRMS calcd for $C_{18}H_{15}N_2O_2$ ([M−$C_{11}H_{16}NO_3S$]$^+$) 291.1133 found 291.1114.

3.6.5. [1*R*-[1β(3a*R,6*S**,7a*S**),3β,3aα,6aα]]-3*H*-3a,6-Methano-2,1-benzisothiazole, 7,7-dichloro-4,5,6,7-tetrahydro-8,8-dimethyl-1-[(hexahydro-4,6-dioxo-3,5-diphenylpyrrolo[3,4-*c*]pyrrol-1-yl)carbonyl]-2,2-dioxide (39b).** Flash chromatography (SiO_2 2:1 hexanes/EtOAc) total yield of the cycloadducts 64%; R_f 0.36 (1:1 hexanes/EtOAc); mp=253–254°C; $[\alpha]_D^{27}$=+71° (*c*=1.2, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 7.45–7.20 (10 H, 2×Ph), 4.73 (d, *J*=7.9 Hz, 1H. H-1), 4.67 (d, *J*=8.1 Hz, 1H, H-3), 4.59 (s, 1H, H-7a), 4.21 (t, *J*=7.9 Hz, 1H, H-6a), 3.67 (t, *J*=8.0 Hz, 1H, H-3a), 3.61 (d, *J*=14 Hz, 1H, 1/2CH_2SO_2), 3.56 (d, *J*=14 Hz, 1H, 1/2CH_2SO_2), 2.89 (t, *J*=8.0 Hz, 1H, N–H), 2.57 (d, *J*=4.5 Hz, 1H), 2.41 (1H), 2.02 (2H), 1.60 (1H), 1.51 (s, 3H, CH_3), 1.11 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$) δ 174.8, 173.7, 169.8, 135.6, 131.7, 129.0 (2C), 128.5 (2C), 128.3 (2C), 127.1 (2C), 126.4 (2C), 93.4, 79.3, 65.7, 63.6, 62.3, 52.67, 51.0, 50.9, 50.4, 49.5, 31.7, 25.3, 24.7, 23.0; IR ($CHCl_3$) cm^{-1} 3000 (m), 1720 (s), 1340 (s), 1220 (s); HRMS calcd for $C_{18}H_{15}N_2O_2$ ([M−$C_{11}H_{14}NO_3SCl_2$]$^+$), 291.1134 found 291.1133.

3.6.6. [1*R*-[1α(3a*R,6*S**,7a*S**),3α,3aβ,6aβ]]-3*H*-3a,6-Methano-2,1-benzisothiazole, 7,7-dichloro-4,5,6,7-tetrahydro-8,8-dimethyl-1-[(hexahydro-4,6-dioxo-3,5-diphenylpyrrolo[3,4-*c*]pyrrol-1-yl)carbonyl]-2,2-dioxide (40b).** R_f 0.60, (1:1 hexanes/EtOAc); $[\alpha]_D^{27}$=−19° (*c*=1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 7.60–7.28 (10 H, 2×Ph), 4.72 (d, *J*=6.6 Hz, 1H, H-1), 4.56 (s, 1H, H-7a), 4.53 (d, *J*=7.7 Hz, 1H, H-3), 3.99 (dd, *J*=9.7, 6.8 Hz, 1H, H-6a), 3.58 (d, *J*=14 Hz, 1H, 1/2CH_2SO_2), 3.54 (dd, *J*=9.8, 7.0 Hz, 1H, H-3a), 3.51 (d, *J*=14 Hz, 1H, 1/2CH_2SO_2), 3.28 (br s, 1H, N–H), 2.59 (d, *J*=4.27 Hz, 1H), 2.45 (1H), 2.02 (2H), 1.62 (2H), 1.56 (s, 3H, CH_3), 1.10 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$) δ 175.0, 173.7, 172.3, 139.6, 131.5, 129.2 (2C), 128.8 (2C), 128.7, 127.1 (2C), 126.6 (2C), 126.4, 78.7, 66.3, 62.8, 62.2, 53.8, 52.9, 52.1, 50.7, 49.7, 31.7, 29.8, 25.4, 24.3, 23.0; IR ($CHCl_3$) cm^{-1} 3010 (m), 1730 (s, C═O), 1340 (s), 1220 (s), 1140 (m), 1060 (m), 900 (m); HRMS calcd for $C_{18}H_{15}N_2O_2$ ([M−$C_{11}H_{14}NO_3SCl_2$]$^+$), 291.1134, found 291.1137.

3.6.7. 3*H*-3a,6-Methano-2,1-benzisothiazole, 7,7-dichloro-4,5,6,7-tetrahydro-8,8-dimethyl-1-[(hexahydro-4,6-dioxo-3,5-diphenylpyrrolo[3,4-*c*]pyrrol-1-yl)carbonyl]-2,2-dioxide (41b). R_f 0.40 (1:1 hexanes/EtOAc); mp=170–172°C; $[\alpha]_D^{27}=+86°$ (c=0.9, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 7.45–7.10 (10 H, 2×Ph), 5.23 (s, 1H, H-1), 5.12 (d, J=9.2 Hz, 1H, H-3), 4.51 (s, 1H, H-7a), 3.79 (d, J=7.7 Hz, 1H, H-6a), 3.68 (dd, J=9.2, 7.9 Hz, 1H, H-3a), 3.60 (d, J=14 Hz, 1H, 1/2CH_2SO_2), 3.53 (d, J=14 Hz, 1H, 1/2CH_2SO_2), 2.88 (br s, 1H, N–H), 2.62 (d, J=4.3 Hz, 1H), 2.45 (1H), 2.04 (2H), 1.61 (1H), 1.53 (s, 3H, CH_3), 1.13 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$) δ 175.4, 174.3, 172.8, 138.5, 131.9, 129.0 (2C), 128.5 (2C), 128.4, 127.5 (2C), 126.1 (2C), 93.6, 78.7, 62.9, 62.2, 62.2, 52.7, 51.1, 50.5, 49.7, 49.2, 31.7, 29.8, 25.5, 24.4, 22.9; IR ($CHCl_3$) cm^{-1} 3000 (m), 1720 (s), 1340 (s), 1220 (s); HRMS calcd for $C_{18}H_{15}N_2O_2$ ([M−$C_{11}H_{14}NO_3SCl_2$]$^+$), 291.1134, found 291.1126.

3.6.8. [3a*R*-[1(2*S,3*R**,5*R**),3aα,6α,7aβ]]-3-Pyrrolidinecarboxylic acid, 2-phenyl-5-[(tetrahydro-8,8-dimethyl-3*H*-3a,6-methano-2,1-benzisothiazol-1(4*H*)-yl)carbonyl]-methyl ester, *S*,*S*-dioxide (42a).** Flash chromatography (SiO_2, 2:1 hexanes/EtOAc); total yield of the cycloadducts 64%; R_f 0.46 (1:1 hexanes/EtOAc); ^1H NMR ($CDCl_3$) δ 7.38–7.20 (5H, Ph), 4.55 (d, J=8.1 Hz, 1H, H-2), 4.45 (t, J=8.3 Hz, 1H, H-5), 3.97 (dd, J=5.5, 1.7 Hz, 1H, H-7a), 3.52 (d, J=14 Hz, 1H, 1/2CH_2SO_2), 3.45 (d, J=14 Hz, 1H, 1/2CH_2SO_2), 3.37 (dd, J=7.90, 6.84 Hz, 1H, H-3), 3.20 (s, 3H, OCH_3), 2.60 (dt, J=7.9, 7.9 Hz, 1H, H-4), 2.28 (ddd, J=13.1, 8.5, 1.8 Hz, 1H, H-4), 2.16 (2H), 1.90 (br s, 3H), 1.50–1.35 (3H), 1.15 (s, 3H, CH_3), 0.97 (s, 3H, CH_3); ^{13}C NMR (C_6D_6) δ 172.9, 172.2, 139.9, 128.3 (2C), 127.6, 127.2 (2C), 66.0, 65.0, 61.4, 52.4, 50.5, 50.2, 48.2, 47.4, 44.5, 38.2, 35.7, 32.0, 26.2, 20.7, 19.4; IR ($CHCl_3$) cm^{-1} 3680 (w), 3000 (s), 2450 (m), 2400 (w), 1720 (s, C=O), 1690 (s), 1330 (s), 1270 (m), 1210 (s), 1160 (s), 1130(s); HRMS calcd for $C_{23}H_{29}N_2O_5S$ ([M−H]$^+$) 445.1797, found 445.1779.

3.6.9. [3a*R*-[1(2*S,3*R**,5*R**),3aα,6α,7aβ]]-3-Pyrrolidinecarboxylic acid, 2-phenyl-5-[(7,7-dichloro-4,5,6,7-tetrahydro-8,8-dimethyl-3*H*-3a,6-methano-2,1-benzisothiazol-1(4*H*)-yl)carbonyl]-methyl ester, *S*,*S*-dioxide (42b).** Flash chromatography (SiO_2, 2:1 hexanes/EtOAc); total yield of the cycloadducts 58%; R_f 0.40 (1:1 hexanes/EtOAc); $[\alpha]_D^{27}=+14°$ (c=3, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 7.40–7.20 (5H, Ph), 4.60 (dd, J=9.3, 7.8 Hz, 1H, H-5), 4.58 (d, J=8.2 Hz, 1H, H-2), 4.55 (s, 1H, H-7a), 3.54 (s, 2H, 1/2CH_2SO_2), 3.43 (dd, J=17, 7.9 Hz, 1H, H-3), 3.21 (s, 3H, OCH_3), 2.68–2.42 (5H), 2.02 (2H), 1.65 (1H), 1.48 (s, 3H, CH_3), 1.10 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$) δ 173.3, 172.5, 139.3, 128.2 (2C), 127.6, 127.0 (2C), 93.5, 78.5, 65.2, 62.3, 61.6, 52.6, 51.4, 50.8, 50.4, 49.6, 34.6, 31.5, 25.4, 24.1, 22.9; IR ($CHCl_3$) cm^{-1} 3010 (m), 1730 (s), 1340 (s), 1220 (s), 1140 (m), 1060 (m), 900 (m); HRMS calcd for $C_{12}H_{14}NO_2$ ([M−$C_{11}H_{14}NO_3SCl_2$]$^+$) 204.1025, found 204.1026.

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