Stereoselectivity in the $TiCl_4$-Catalyzed [4 + 2] Cycloaddition of Cyclopentadiene to (2*R*)-Bornane-10,2-sultam Derivatives of Fumaric Acid Monoesters[1])

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The [4 + 2] cycloaddition of cyclopentadiene to the (2*R*)-bornane-10,2-sultam derivative (−)-**1b** of fumaric monomethyl ester proceeds with high *endo* and π-facial diastereoselectivity in the presence of 0.5 mol-equiv. of $TiCl_4$. The major diastereoisomer *endo*-(2*R*,3*R*)-**2b**, isolated in 87% yield by crystallization, was subjected to X-ray crystal-structure analysis. Steric influence of ethyl- and benzyl-ester analogues (−)-**1c** and (−)-**1d**, respectively, is also reported.

Introduction. – We recently presented the complete π-facial selectivity observed in the $TiCl_4$-catalyzed [4 + 2] cycloaddition of cyclopentadiene to *N*,*N*′-fumaroylbis[(2*R*)-bornane-10,2-sultam] ((−)-**1a**) [1] under the influence of diverse *Lewis* acids, as well as its application to diverse dienes [2]. Although these kinds of cycloadducts have been employed for the synthesis of several natural products [3] and analogues [4], their use is usually limited to symmetric or specific targets where the two carbonyl moieties can be distinguished by either iodolactonization [5] or selective steric approach of the reagent[3]). For this reason, nonsymmetrical chiral fumarates were earlier developed [9][4]), where one carbonyl moiety may be chemoselectively transposed into a suitable functionality, either by selective saponification [9b], acidic hydrolysis [12], hydrogenation [13], or hydride reduction [14][5]). With respect to this methodology, we now would like to present our results obtained with (2*R*)-bornane-10,2-sultam derivatives (−)-**1b**–**d** of fumaric acid monoesters as dienophiles.

Results and Discussion. – The syntheses of crystalline (−)-**1b**,**c** were earlier reported [15][16], while (−)-**1d** was obtained in 83% yield, after crystallization from CCl_4, by addition of the corresponding crude acid chloride (fumaric acid monobenzyl

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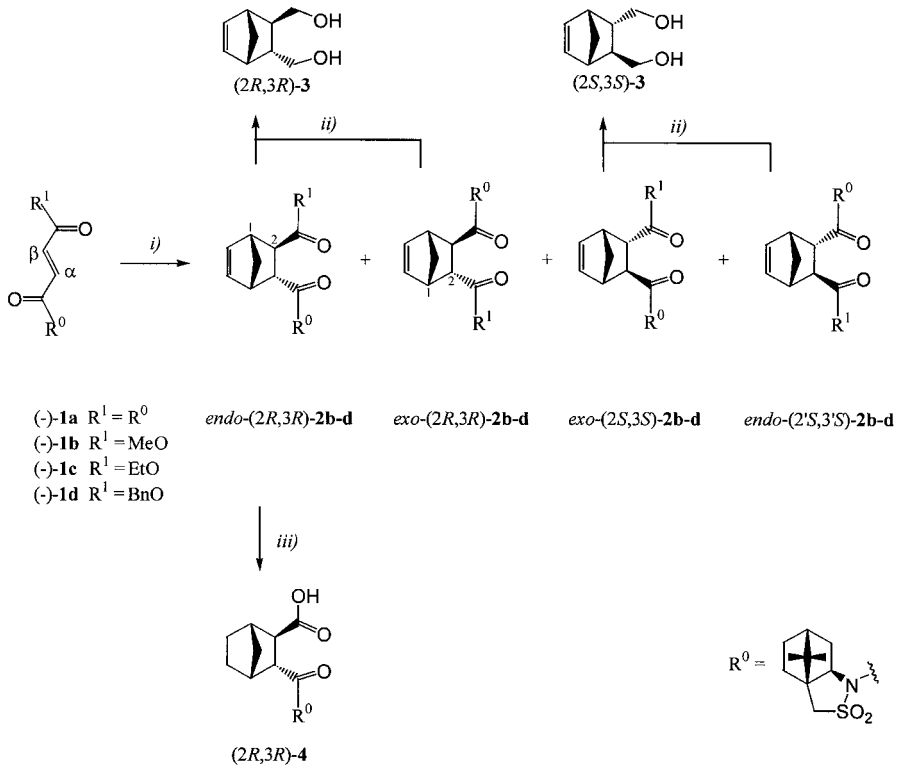
3) For asymmetric [4 + 2] cycloadditions of symmetrical fumarates, see ref. cited in [1] and [2]; for more recent ref., see [6]. For the cycloaddition of achiral symmetric fumarates catalyzed by chiral catalysts, see [7]. For a recent review of asymmetric intermolecular homo- and hetero-*Diels-Alder* reactions, see [8].
4) For achiral dienophiles of this type catalyzed by chiral catalysts, see [10]; for nonsymmetric maleates, see [11].
5) The [4 + 2] cycloadditions of analogous dienophiles derived from nonsymmetrical (2*R*)-bornane-10,2-sultam derivatives (−)-**1** of fumaric acid (R^1 = H, OH, ^{t}BuO, 1*H*-imidazol-1-yl, achiral *N*-substituted toluenesultam) are also envisaged and will be reported in due time.



i) CH_2Cl_2, $-78°$, 20 h, 0.0–2.0 mol-equiv. of $TiCl_4$, 10.0 mol-equiv. of cyclopenta-1,3-diene. *ii*) $LiAlH_4$, THF. *iii*) H_2, 10% (*w*/*w*) Pd/C, EtOH.

ester [17], $(COCl)_2$ (2.0 mol-equiv.), toluene, 80°) to the deprotonated free camphor-derived sultam (NaH, 1.1 mol-equiv., toluene, 0–20° [18]).

For a detailed study of the [4 + 2] cycloaddition, dienophile (−)-**1b** was selected, anticipating a simpler ^{1}H-NMR analysis of the cycloadducts, as well as a potential S_N2' chemospecific saponification of the methoxycarbonyl moiety [19]. The uncatalyzed [4 + 2] cycloaddition of (−)-**1b** to cyclopentadiene (10 mol-equiv.) in CH_2Cl_2 at 20° afforded after 20 h, quantitatively, a 51 : 29 : 12 : 8 mixture of diastereoisomers, as determined by integration of the olefinic protons in the ^{1}H-NMR spectrum of the crude material[6]). Purification by chromatography (SiO_2, hexane/AcOEt 9 : 1) allowed the isolation of a faster eluting minor pair of diastereoisomers as an 8 : 7 mixture (16%; resulting from the 12 : 8 mixture) as well as a more polar major pair of diastereoisomers as a 5 : 2 mixture (75%; resulting from the 51 : 29 mixture).

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[6]) The ^{1}H-NMR analysis of the pure major diastereoisomer shows signals at 6.34 and 5.86 ppm, while its diastereoisomeric partner resonates at 6.34 and 6.14 ppm. The large difference between the two olefinic signals suggests an *endo* orientation of the large sultam moiety for the major diastereoisomer [20]. The third most abundant isomer exhibits signals at 6.31 and 6.17 ppm, as compared to its paired (not isolated pure) diastereoisomer, which shows signals at 6.31 and 6.06 ppm, thus suggesting an *endo*-orientation of the chiral auxiliary in this latter case.

We then decided to perform the reaction at $-78°$ in the presence of increasing quantities of $TiCl_4$. The results, summarized in *Table 1*, show several noteworthy aspects. For example, the uncatalyzed reaction of (−)-**1b** gave a 61 : 24 : 8 : 7 mixture in 46% yield (*Entry 4*), while the diastereoselectivity and the chemical yield were greatly improved by addition of $TiCl_4$ (0.25 mol-equiv., *Entry 7*). The optimal diastereoisomer efficiency was reached for 0.5 mol-equiv. of *Lewis* acid, thus affording in 98% yield a 94 : 3 : 1 : 2 mixture (*Entry 8*). The two major isomers, separated by chromatography from the two minor ones, were further purified by crystallization in EtOH, and the most abundant isomer *endo*-(2*R*,3*R*)-**2b** was obtained pure in 87% yield. The $LiAlH_4$ reduction of the 8 : 7 minor pair of diastereoisomers obtained from the first described reaction at room temperature (*Entry 1*) resulted in the formation of optically pure diol (−)-(2*S*,3*S*)-**3**[7]), after crystallization of the concomitantly formed free sultam (91%) from hexane. The relative and absolute configuration of the main crystalline cycloadduct *endo*-(2*R*,3*R*)-**2b** was confirmed by X-ray crystal-structure analysis showing both the *endo*-orientation of the sultam moiety and the (2*R*,3*R*)-configuration (see *Fig.*).

Table 1. *Cyclopentadiene [4 + 2] Cycloaddition to* (−)-**1b**–**d** *in* CH_2Cl_2 *at* $-78°$ *for 20 h*

Entry	Dienophile	Equiv. of $TiCl_4$	*endo*-(2*R*,3*R*)-**2** [%]	*exo*-(2*R*,3*R*)-**2** [%]	*exo*-(2*S*,3*S*)-**2** [%]	*endo*-(2*S*,3*S*)-**2** [%]	*endo*/*exo* [%]	Yield [%]	Global de [%]	*endo* de [%]	*exo* de [%]
1[a])	(−)-**1b**	0.00	51	29	12	8	59 : 41	98	60	73	41
2[a])	(−)-**1c**	0.00	54	23	12	11	65 : 35	97	54	66	31
3[a])	(−)-**1d**	0.00	49	22	16	13	62 : 38	96	42	58	16
4	(−)-**1b**	0.00	61	24	8	7	68 : 32	46	70	79	50
5	(−)-**1c**	0.00	63	21	8	8	71 : 29	36	68	77	45
6	(−)-**1d**	0.00	54	20	14	12	66 : 34	42	48	64	18
7	(−)-**1b**	0.25	92	5	1	2	94 : 6	97	94	95	67
8	(−)-**1b**	0.50	94	3	1	2	96 : 4	98	94	96	50
9	(−)-**1c**	0.50	92	3	2	3	95 : 5	96	90	94	25
10	(−)-**1d**	0.50	86	3	5	6	92 : 8	98	78	87	−25
11	(−)-**1b**	0.75	93	4	1	2	95 : 5	98	94	96	60
12	(−)-**1b**	1.00	88	5	3	4	92 : 8	95	86	91	25
13	(−)-**1d**	1.00	84	3	7	6	90 : 10	95	74	87	−40
14	(−)-**1b**	1.25	85	6	6	3	88 : 12	96	82	93	0
15	(−)-**1b**	2.00	75	9	11	5	80 : 20	95	68	88	−10

[a]) Reaction performed at 20°.

Similarly, using 0.5 mol-equiv. of $TiCl_4$, **2c,d** were obtained as 92 : 3 : 2 : 3 and 86 : 3 : 5 : 6 mixtures (*Table 1*, *Entry 9* and *10*, resp.). In both cases, the chromatographically purified major more polar inseparable pair of diastereoisomers was recrystallized from EtOH to afford pure *endo*-(2*R*,3*R*)-**2c,d** in 80 and 73% yield, respectively[8]).

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[7]) (−)-(2*S*,3*S*)-**3**: $[\alpha]_D^{20} = -23.1$ ($c = 1.01$, $CHCl_3$) ([21]: $[\alpha]_D^{20} = -24.7$ ($c = 0.8$)). Similarly, reduction of the 96 : 4 mixture obtained after chromatographic purification of the most abundant pair (*Entry 8*; 95%), afforded (+)-(2*R*,3*R*)-**3**; $[\alpha]_D^{20} = +23.6$ ($c = 1.1$, $CHCl_3$) ([22]: $[\alpha]_D^{20} = +23.0$ ($c = 0.6$)).

[8]) Reduction to optically pure (+)-(2*R*,3*R*)-**3** ($[\alpha]_D^{20} = +23.8$ ($c = 1.2$, $CHCl_3$)) confirmed the absolute configuration of *endo*-(2*R*,3*R*)-**2c,d**. That of the other diastereoisomers of **2c,d** was based on ^{1}H-NMR comparison with the diastereoisomers of **2b** (see *Exper. Part*).

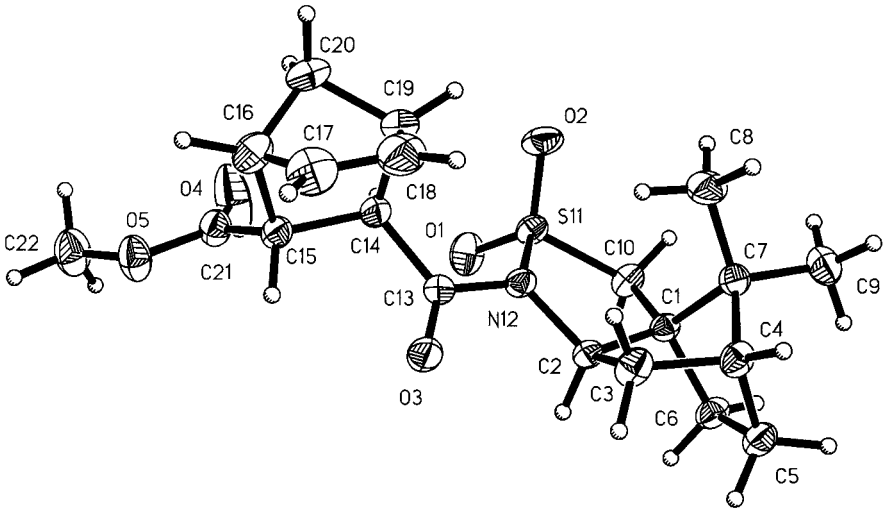

Figure. *ORTEP Diagram of* **2b** *showing* endo-*(2*R,*3*R*)-configuration*. Thermal ellipsoids at 50% probability level; arbitrary numbering.

In the case of the symmetrical dienophile (–)-**1a**, a mixture of diastereoisomers (85% de) was observed at 20°, while this ratio increased to 89% de at –78° for the uncatalyzed reaction in CH_2Cl_2 [1]. Thus, the 73% de observed during the *endo* addition of dienophile (–)-**1b** at 20° (*Entry 1*), bearing a single prosthetic group, is much higher than the theoretical $(92.5:7.5)^{1/2} = 56\%$ de expected according to the cooperative postulate of *Tolbert* and *Ali* [23]. This difference is even accentuated at –78°, since the 79% de obtained for *endo*-**2b** (*Entry 4*) should be compared with the theoretical $(94.5:5.5)^{1/2} = 61\%$ de expected. As recently shown, this difference may depend on either the solvent [24] or the steric/electronic influence of the residual group branched to the C(β)-atom of the dienophile [15a]. Thus, the diastereoselectivity observed for the *endo* attack on the ethyl- and benzyl-ester analogues (–)-**1c,d** decreases for these sterically more demanding esters[9]). This is logical, since the π-face selectivity of this kind of dienophile is partially steric in origin [18][25]; thus, such a trend is also observed for both *endo* and *exo* (catalyzed) [4 + 2] cycloaddition to (–)-**1b–d** (*Entries 8–10*). The ester substituent may not only sterically influence the approach of the diene, but may also modify the coplanarity of the dienophile as well as its intrinsic electronic properties. Intuitively, from a purely steric point of view, the *endo*/*exo* ratio should increase with increasing steric bulk of the ester substituent. Nevertheless, the contrary is observed, at least in the case of the catalyzed reactions (*Entries 8–10*), indicating a possible electronic contribution.

For (–)-**1b**, the *endo*/*exo* ratio proportionally increases until the addition of 0.5 mol-equiv. of *Lewis* acid, and then starts to decrease with concomitant weakening of

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[9]) For the *endo* approach to (–)-**1c**, the diastereoselectivity of 66% at 20° (*Entry 2*) and of 77% at –78° (*Entry 5*) diminishes, while for (–)-**1d**, the diastereoselectivity of 58% at 20° (*Entry 3*) and of 64% at –78° (*Entry 6*) is even closer to the theoretical value. Formally, the correct comparison should be done with an achiral sultam residue for R^1.

the global π-facial selectivity (*Entries 4, 7, 8, 11, 12, 14,* and *15*). This ratio even reaches, for 2.0 mol-equiv. of $TiCl_4$ (*Entry 15*), a similar global diastereoselectivity (global de) as observed for the uncatalyzed reaction (*Entry 4*). At catalytic levels, we assume that $TiCl_4$ prefers to be chelated to the SO_2/C=O functionalities of the bornane-10,2-sultam auxiliary [18][26], rather than simply coordinated to the methoxycarbonyl moiety[10]), thus promoting *endo* addition with respect to the sultam carbamoyl moiety. By increasing the *Lewis*-acid concentration to 1 equiv. and above, the methoxycarbonyl group starts to be coordinated, and the differences in the second-order orbital interactions between cyclopentadiene and both carbonyl moieties decreases, resulting in a sterically more favorable competitive *endo* attack with respect to the methoxycarbonyl substituent. The diene, thus removed from the prosthetic group, shows much lower π-facial discrimination in the *exo* approach[11]). Based on earlier work [18][25][27] as well as on X-ray analysis of a $TiCl_4$-sultam complex [26], we propose that the C=C bond is conformationally s-*cis*-restricted with respect to the C=O/SO_2 *syn*-chelated moieties of the sultam, thus offering its C(α)-*re* face to the sterically and stereoelectronically preferred *endo* attack [28]. In the uncatalyzed case, the same face is prone to *endo* addition [28][12]), the methoxycarbonyl group, being slightly more stable in a s-*cis*-conformation with respect to the reactive C=C bond, may change to a s-*trans* conformation in case of competitive coordination with $TiCl_4$. This supplementary/competitive coordination may even destabilize the conformational equilibrium or sterically interfere with the incoming diene, thus additionally providing a tentative explanation for the lower diastereoselectivity observed in the presence of more than 1.0 mol-equiv. of $TiCl_4$ for both *endo* and *exo* modes of addition. In the latter case, the diastereoselectivity even starts to reverse in the presence of 2.0 mol-equiv. of $TiCl_4$ (*Entry 15*), or for the sterically more demanding benzyl ester (−)-**1d** (*Entries 10* and *13*).

Finally, we hydrogenated (H_2, 10% (*w*/*w*) Pd/C, 98% EtOH) *endo*-(2*R*,3*R*)-**2d** to the saturated mono-acid (2*R*,3*R*)-**4**, thus demonstrating the clear synthetic advantage of nonsymmetrical fumaric-acid-derived dienophiles of type (−)-**1b**–**d**[5]).

The X-ray analysis of *endo*-(2*R*,3*R*)-**2b** (see *Table 2* for selected structural parameters) exhibits the usual features of such *N*-acylbornane-10,2-sultams [18], such as the *anti*-periplanar disposition of the SO_2/C(=O) moieties, with concomitant anomeric pyramidalization of the N-atom [28][13]).

Conclusion. – High diastereoselectivity (87–96%) was obtained during the $TiCl_4$-catalyzed (0.5 mol-equiv.) *endo* addition of (−)-**1b**–**d** to cyclopentadiene. Chromato-

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10) Chelation is also entropically more favorable than the intermolecular dicoordination to two methoxycarbonyl functionalities.

11) In case of the catalyzed cyclopentadiene [4+2] cycloaddition to monomenthyl methyl fumarate, preferential *endo* attack with respect to the sterically less demanding methoxycarbonyl group was earlier observed [9d]; this selectivity was even increased to 98.4% in the presence of a sterically demanding catalyst.

12) Recent PM3 calculations of (−)-**1b** LUMO suggest that the steric/stereoelectronic effects are cooperative only for the C(α)-atom in its *syn*-s-*cis*-conformation [15a].

13) For a recent discussion of the influence of the pyramidalization on the sp^3 N overlap with the carbonyl moiety and resultant reactivity in anomeric amides and sultams, see [29].

Table 2. *Selected Bond Lengths* [Å] *and Angles* [°] *for* endo-*(2*R*,3*R*)*-**2b** (lp = lone electron pair)

*Δh*N	0.200(4)	S–N–C(13)–O(3)	154.6(3)
S–O(1)	1.430(2)	O(1)–S–N–C(2)	107.1(2)
S–O(2)	1.422(3)	O(2)–S–N–C(2)	– 123.2(2)
S–N	1.692(2)	O(1)–S–N–lp	– 151.5(2)
O(1)–S–O(2)	117.2(2)	O(2)–S–N–lp	– 21.8(2)

graphic separation of the *endo*/*exo*-(2*R*,3*R*)-**2b**–**d** from the minor *endo*/*exo*-(2*S*,3*S*) pair of diastereoisomers led, after crystallization and reduction with $LiAlH_4$, to optically pure (2*R*,3*R*)-**3** in 91–93% yield, with non-destructive removal of the chiral auxiliary (89–91%). Nonsymmetric, optically pure cycloadducts of type *endo*-**2b**–**d** are ideal building blocks for the synthesis of diverse molecules possessing potent antithrombotic [30] or A_2/prostaglandin endoperoxide receptor antagonist properties [31], as well as of loganin [32] and nitraraine alkaloids [33]. This methodology may also be applied to the preparation of the hexahydrobenzofuran subunit of the avermectins and milbemycins [34] and to the marine diterpene fuscol [35].

We are indebted to Dr. *Zofia Urbañczyk-Lipkowska* for X-ray analysis and structure determination of (2*R*,3*R*)-**2b**. Financial support from the *Polish Academy of Sciences* and from the University of Warsaw (BST/592/18/98) is gratefully acknowledged.

Experimental Part

General. See [15a].

X-Ray Crystal-Structure Determination of endo-(2R,3R)-**2b**. Crystal data and measurement conditions are given in *Table 3*. Diffraction data were collected at r.t. on a four-circle *Enraf-Nonius-MACH3* diffractometer using 'Express' software, without absorption correction. Monochromated CuK_α radiation (λ 1.54178 Å) was applied, and the ω-2θ scan technique was used during measurements. In the final steps of the least-squares procedure, all but the Me group H-atoms were kept fixed at their calculated positions. The structure was solved by the SHELXS [36] and refined with the SHELXL [37] programs. Crystallographic data for *endo*-(2*R*,3*R*)-**2b** have been deposited at the *Cambridge Crystallographic Data Center* as supplementary publication No CCDC-102389.

Table 3. *Crystal Data and Structure Refinement of* endo-*(2*R*,3*R*)*-**2b**

Empirical formula	$C_{20}H_{27}NO_5S$	θ-Range [°]	3.51 to 73.65
Formula weight	393.49	Index ranges	$0 < h < 9$, $0 < k < 12$, $0 < l < 31$
Crystal system	orthorhombic	Reflex. collected	2073
Space group	$P2_12_12_1$	Independent reflex	2070 (R(int) = 0.0335)
Unit cell dimension a [Å]	7.889(6)	Completeness to $2\theta = 73.65$	91.8%
b [Å]	9.7412(4)	Refinement method	Full-matrix least-square on F_2
c [Å]	25.2030(10)	Data/restraints/parameters	2070/0/245
Volume [Å^3]	1936.7(15)	goodness of fit on F_2	1.053
Z	4	Final R indices ($I > 2\sigma(I)$)	$R_1 = 0.0371$, $wR_2 = 0.1094$
Density calc. [Mg m^{-3}]	1.350	R indice (all data)	$R_1 = 0.0379$, $wR_2 = 0.1105$
Absorption coeff. [mm^{-1}]	1.751	Absolute structure parameter	– 0.07(3)
F(000)	840	Extinction coeff.	0.0014(3)
Crystal size [mm]	0.7 × 0.63 × 0.56	Largest diff. peak and hole [e · Å^{-3}]	0.229 and – 0.207

*(–)-(2*R*)-*N*-[(*E*)-3-[(Benzyloxy)carbonyl]prop-2-enoyl]bornane-10,2-sultam* (= *(–)-Benzyl* (E)*-4-[(3a*S*,6*R*,7a*R*)-1,4,5,6,7,7a-Hexahydro-8,8-dimethyl-2,2-dioxido-3*H*-3a,6-methano[2,1]benzisothiazol-1-yl]-4-oxobut-2-enoate*; (–)-**1d**). To a stirred suspension of NaH (225 mg, 4.52 mmol; 50% in mineral oil, washed 3 × with dry pentane) in dry toluene (35 ml) (2*R*)-bornane-10,2-sultam (972 mg, 4.52 mmol) in toluene (15 ml) was added.

After 30 min at r.t., freshly prepared crude benzyl (*E*)-4-chloro-4-oxobut-2-enoate in toluene (10 ml) (obtained after distillative concentration of an excess of oxalyl chloride (1370 mg, 10.8 mmol) and fumaric acid monobenzyl ester [17] (1120 mg, 5.4 mmol) in toluene (15 ml), 80°, 1 h) was added dropwise at 0°, and the mixture was stirred at r.t. for 18 h. The reaction was quenched by addition of sat. aq. NH_4Cl soln. (40 ml) and extracted with toluene (4 × 20 ml). The org. phase was dried ($MgSO_4$) and evaporated and the residue purified by CC (cyclohexane/AcOEt 9 : 1): pure (−)-**1d** (85%). White solid. M.p. 126–128° (CCl_4, 83%). $[\alpha]_D^{20} = -111.1$ ($c = 1.5$, CCl_4). IR: 2957, 1724, 1679, 1292, 1161, 1134, 1066, 971. ^{1}H-NMR: 0.98 (*s*, 3 H); 1.17 (*s*, 3 H); 1.4 (*m*, 2 H); 1.9 (*m*, 3 H); 2.15 (*m*, 2 H); 3.51 (*q*, $J = 14$, 2 H); 3.96 (*dd*, $J = 6$, 8, 1 H); 5.24 (*AB*, $J = 12$, 16, 2 H); 6.95 (*d*, $J = 16$, 1 H); 7.37 (*m*, 5 H); 7.6 (*d*, $J = 16$, 1 H). ^{13}C-NMR: 19.9 (*q*); 20.8 (*q*); 26.5 (*t*); 32.9 (*t*); 38.3 (*t*); 44.7 (*d*); 47.9 (*s*); 48.8 (*s*); 53.0 (*t*); 65.1 (*d*); 67.1 (*t*); 128.3 (2*d*); 128.4 (*d*); 128.6 (2*d*); 132.8 (*d*); 133.7 (*d*); 135.3 (*s*); 162.4 (*s*); 164.4 (*s*). MS: 403 (0, $M^{+\bullet}$), 358 (4), 297 (26), 233 (25), 135 (21), 91 (100), 79 (6).

*(2*R*,3*R*)-3-{[(3a*S*,6*R*,7a*R*)-1,4,5,6,7,7a-Hexahydro-8,8-dimethyl-2,2-dioxido-3*H*-3a,6-methano[2,1]benzisothiazol-1-yl]carbonyl}bicyclo[2.2.1]hept-5-ene-2-carboxylic Acid Methyl Ester* (*endo*-(2*R*,3*R*)-**2b**). To a soln. of (−)-**1b** (327 mg, 1.0 mmol) in CH_2Cl_2 (20 ml), 1M $TiCl_4$ in CH_2Cl_2 (0.5 ml, 0.5 mmol) was added. The mixture was cooled to −78° and pre-cooled 1M cyclopenta-1,3-diene in CH_2Cl_2 (10 ml, 10 mmol) was added dropwise and slowly along the interior cold surface of the reaction flask. After 18 h, the reaction was quenched with NH_4F and equilibrated. After addition of H_2O, the mixture was extracted with CH_2Cl_2 and the extract dried ($MgSO_4$) and evaporated under medium and then high vacuum. ^{1}H-NMR analysis showed full conversion and a 94 : 3 : 1 : 2 mixture of cycloadducts. Chromatography (SiO_2, hexane/AcOEt 95 : 5 → 8 : 2) afforded a faster eluting pair of diastereoisomers (8 : 7 mixture; 1.8%) and a more polar pair of diastereoisomers (96 : 4 mixture; 95%) which was recrystallized to afford pure *endo*-(2*R*,3*R*)-**2b** (87%). White solid, M.p. 190–192° (EtOH). $[\alpha]_D^{20} = -219.94$ ($c = 1.03$, $CHCl_3$). IR: 3060, 3000, 2953, 2913, 2881, 1733, 1687, 1328, 1136, 551. ^{1}H-NMR: 0.97 (*s*, 3 H); 1.19 (*s*, 3 H); 1.30–1.75 (*m*, 5 H); 1.80–2.1 (*m*, 4 H); 2.88 (*dd*, $J = 1.4$, 4.4, 1 H); 3.18 (*m*, 1 H); 3.48 (*AB*, $J = 13.7$, 2 H); 3.51 (*m*, 1 H); 3.68 (*s*, 3 H); 3.86 (*m*, 2 H); 5.86 (*dd*, $J = 2.5$, 5.3, 1 H); 6.34 (*dd*, $J = 3.2$, 5.3, 1 H). ^{13}C-NMR: 20.1 (*q*); 20.9 (*q*); 26.6 (*t*); 32.9 (*t*); 38.7 (*t*); 44.8 (*d*); 45.8 (*t*); 46.3 (*d*); 47.7 (*s*); 48.1 (*d*); 48.5 (*s*); 48.7 (*d*); 49.3 (*d*); 52.2 (*q*); 53.3 (*t*); 65.5 (*d*); 133.0 (*d*); 138.5 (*d*); 172.0 (*s*); 174.6 (*s*). HR-MS: 393.16074 ($C_{20}H_{27}NO_5S^+$; calc 393.16099). MS: 393 (1, $M^{+\bullet}$), 362 (3), 328 (18), 296 (14), 178 (65), 150 (25), 135 (35), 113 (100), 66 (30).

*(2*R*,3*R*)-3-{[(3a*S*,6*R*,7a*R*)-1,4,5,6,7,7a-Hexahydro-8,8-dimethyl-2,2-dioxido-3*H*-3a,6-methano[2.1]benzisothiazol-1-yl]carbonyl}bicyclo[2.2.1]hept-5-ene-2-carboxylic Acid Ethyl Ester* (*endo*-(2*R*,3*R*)-**2c**). Obtained in 80% yield, similarly to *endo*-(2*R*,3*R*)-**2b**. M.p. 170–172° (EtOH). $[\alpha]_D^{20} = -209.3$ ($c = 0.7$, CCl_4). IR: 2957, 1726, 1688, 1456, 1392, 1327, 1234, 1209, 1039. ^{1}H-NMR: 0.99 (*s*, 3 H); 1.21 (*s*, 3 H); 1.25 (*t*, $J = 7$, 3 H); 1.30–1.75 (*m*, 5 H); 1.80–2.1 (*m*, 4 H); 2.88 (*dd*, $J = 1.4$, 4.4, 1 H); 3.22 (br. *s*, 1 H); 3.48 (*AB*, $J = 14$, 2 H); 3.51 (*m*, 1 H); 3.87 (*m*, 2 H); 4.16 (*m*, 2 H); 5.86 (*dd*, $J = 2.5$, 5.3, 1 H); 6.34 (*dd*, $J = 3.2$, 5.3, 1 H). ^{13}C-NMR: 14.2 (*q*); 19.9 (*q*); 20.8 (*q*); 26.5 (*t*); 32.7 (*t*); 38.5 (*t*); 44.6 (*d*); 45.8 (*t*); 46.3 (*d*); 47.5 (*d*); 47.8 (*s*); 47.9 (*d*); 48.5 (*s*); 49.2 (*d*); 53.2 (*t*); 60.8 (*t*); 65.3 (*d*); 132.8 (*d*); 138.4 (*d*); 172.0 (*s*); 174.0 (*s*). MS: 407 (0, $M^{+\bullet}$), 341 (4), 296 (21), 268 (22), 231 (21), 204 (45), 150 (29), 135 (35), 127 (100), 99 (32), 55 (16).

The paired diastereoisomer *exo*-(2*R*,3*R*)-**2c** exhibits signals at 6.34 and 6.14 ppm in the ^{1}H-NMR spectrum, while the *exo*-(2*S*,3*S*)-**2c** diastereoisomer resonates at 6.32 and 6.19 ppm, when compared to its inseparable *endo*-(2*S*,3*S*)-**2c** counterpart (6.32 and 6.03 ppm for olef. H).

*(2*R*,3*R*)-3-{[(3a*S*,6*R*,7a*R*)-1,4,5,6,7,7a-hexahydro-8,8-dimethyl-2.2-dioxido-3*H*-3a,6-methano[2,1]benzisothiazol-1-yl]carbonyl}bicyclo[2.2.1]hept-5-ene-2-carboxylic Acid Benzyl Ester* (*endo*-(2*R*,3*R*)-**2d**). Obtained in 73% yield, similarly to *endo*-(2*R*,3*R*)-**2b**. M.p. 143–144° (EtOH). $[\alpha]_D^{20} = -148.4$ ($c = 2.6$, $CHCl_3$). IR: 2957, 1730, 1688, 1330, 1269, 1234, 1209, 1163, 1132, 1053, 782, 754. ^{1}H-NMR: 0.98 (*s*, 3 H); 1.19 (*s*, 3 H); 1.35 (*m*, 2 H); 1.47 (*m*, 1 H); 1.71 (br. *d*, $J = 8$, *1* H); 1.9 (*m*, 4 H); 2.0 (*m*, 1 H); 2.94 (*dd*, $J = 3$, 6, 1 H); 3.2 (br. *s*, 1 H); 3.5 (*q*, $J = 14$, 2 H); 3.53 (br. *s*, 1 H); 3.86 (*dd*, $J = 4$, 8, 1 H); 3.95 (*t*, $J = 4$, 1 H); 5.14 (*AB*, $J = 12$, 2 H); 5.88 (*dd*, $J = 3$, 6, 1 H); 6.34 (*dd*, $J = 3$, 6, 1 H); 7.35 (*m*, 5 H). ^{13}C-NMR: 19.9 (*q*); 20.8 (*q*); 26.5 (*t*); 32.7 (*t*); 38.5 (*t*); 44.6 (*d*); 46.3 (*d*); 47.8 (*d*); 47.8 (*s*); 48.0 (*d*); 48.3 (*s*); 48.4 (*t*); 49.1 (*d*); 53.1 (*t*); 65.3 (*d*); 66.6 (*t*); 128.0 (*d*); 128.1 (2*d*); 128.5 (2*d*); 132.9 (*d*); 136.0 (*s*); 138.3 (*d*); 171.8 (*s*); 173.8 (*s*). MS: 469 (0, $M^{+\bullet}$), 358 (3), 297 (26), 233 (25), 135 (23), 91 (100), 79 (7).

The paired diastereoisomer *exo*-(2*R*,3*R*)-**2d** exhibits signals at 6.34 and 6.04 ppm in the ^{1}H-NMR spectrum, while the *exo*-(2*S*,3*S*)-**2d** diastereoisomer resonates at 6.32 and 6.12 ppm, when compared to its inseparable *endo*-(2*S*,3*S*)-**2d** counterpart (6.32 and 6.02 ppm for olef. H).

Cycloadduct exo-*(2*R*,3*R*)-**2b**. ^{1}H-NMR (deduced from the mixture): 0.99 (*s*, 3 H); 1.20 (*s*, 3 H); 3.09 (*m*, 1 H); 3.26 (*m*, 1 H); 3.62 (*s*, 3 H); 6.14 (*dd*, $J = 2.4$, 5.4, 1 H); 6.34 (*dd*, $J = 2.4$, 5.4, 1 H). ^{13}C-NMR (deduced

from the mixture): 20.1 (*q*); 21.0 (*q*); 26.6 (*t*); 33.0 (*t*); 38.8 (*t*); 45.5 (*d*); 45.9 (*t*); 46.9 (*d*); 47.9 (*s*); 48.0 (*d*); 48.5 (*s*); 49.1 (*d*); 49.8 (*d*); 51.9 (*q*); 53.2 (*t*); 65.5 (*d*); 135.9 (*d*); 137.7 (*d*); 172.6 (*s*); 173.6 (*s*).

Cycloadduct exo-*(2*S*,3*S*)*-**2b**. ^{1}H-NMR (deduced from the mixture): 0.97 (*s*, 3 H); 1.17 (*s*, 3 H); 1.20–1.50 (*m*, 4 H); 1.70 (*m*, 1 H); 1.8–2.0 (*m*, 2 H); 2.0–2.2 (*m*, 2 H); 3.10 (*dd*, *J* = 1.4, 5.0, 1 H); 3.15–3.25 (*m*, 2 H); 3.605 (*s*, 3 H); 6.17 (*dd*, *J* = 1.9, 5.6, 1 H); 6.31 (*dd*, *J* = 2, 5.6, 1 H). ^{13}C-NMR (deduced from the mixture): 20.1 (*q*); 20.9 (*q*); 26.6 (*t*); 33.1 (*t*); 38.8 (*t*); 44.9 (*d*); 46.1 (*t*); 47.2 (*d*); 48.1 (*s*); 48.4 (*d*); 48.5 (*s*); 48.6 (*d*); 50.0 (*d*); 51.9 (*q*); 53.3 (*t*); 65.7 (*d*); 136.1 (*d*); 138.1 (*d*); 172.7 (*s*); 173.7 (*s*).

Cycloadduct endo-*(2*S*,3*S*)*-**2b**. ^{1}H-NMR (deduced from the mixture): 0.96 (*s*, 3 H); 1.15 (*s*, 3 H); 1.2–1.5 (*m*, 4 H); 1.7 (*m*, 1 H); 1.8–2.0 (*m*, 2 H); 2.0–2.2 (*m*, 2 H); 2.60 (*dd*, *J* = 2, 5.3, 1 H); 3.15–3.25 (*m*, 2 H); 3.675 (*s*, 3 H); 6.06 (*dd*, *J* = 3, 5.5, 1 H); 6.31 (*dd*, *J* = 3, 5.5, 1 H). ^{13}C-NMR (deduced from the mixture): 20.1 (*q*); 20.8 (*q*); 26.6 (*t*); 32.9 (*t*); 38.6 (*t*); 44.7 (*d*); 45.1 (*t*); 47.1 (*d*); 48.0 (*s*); 48.5 (*d*); 48.6 (*s*); 48.8 (*d*); 50.3 (*d*); 52.1 (*q*); 53.2 (*t*); 65.6 (*d*); 134.6 (*d*); 137.0 (*d*); 172.7 (*s*); 173.6 (*s*).

*(2*R*,3*R*)-3-{[(3a*S*,6*R*,7a*R*)-1,4,5,6,7,7a-hexahydro-8,8-dimethyl-2,2-dioxido-3*H*-3a,6-methano[2.1]benzisothiazol-1-yl]carbonyl}bicyclo[2.2.1]heptane-2-carboxylic Acid* ((2*R*,3*R*)-**4**). A soln. of *endo*-(2*R*,3*R*)-**2d** (470 mg, 1.0 mmol) in EtOH (10 ml) was hydrogenated in the presence of 10% Pd/C (47 mg). After 4 h, the soln. was filtered and evaporated under medium and then high vacuum to give quantitatively (2*R*,3*R*)-**4**. White solid. M.p. 250–251° (98% EtOH). $[\alpha]_D^{20} = -138.2$ (*c* = 1.3, $CHCl_3$). IR: 3150, 2954, 1697, 1680, 1458, 1407, 1388, 1296, 1265, 1181, 1040, 930, 848. ^{1}H-NMR: 0.98 (*s*, 3 H); 1.14 (*s*, 3 H); 0.8–1.45 (*m*, 7 H); 1.55 (*m*, 1 H); 1.68 (br. *d*, *J* = 16, 1 H); 1.88 (*m*, 2 H); 2.05 (*m*, 2 H); 2.64 (br. *d*, *J* = 5, 1 H); 2.88 (br. *t*, *J* = 3, 1 H); 3.04 (br. *d*, *J* = 5, 1 H); 3.48 (*AB*, *J* = 14, 2 H); 3.75 (*m*, 1 H); 3.92 (*dd*, *J* = 6, 11, 1 H); 8.6 (br. *s*, 1 H). ^{13}C-NMR: 19.9 (*q*); 20.8 (*q*); 23.6 (*t*); 26.5 (*t*); 28.6 (*t*); 32.7 (*t*); 38.8 (*t*); 39.0 (*t*); 41.5 (*d*); 41.6 (*d*); 44.7 (*d*); 47.7 (*d*); 48.3 (2 *s*); 50.7 (*d*); 53.0 (*t*); 65.3 (*d*); 172.0 (*s*); 179.4 (*s*). EI-MS: 381 (1.5, $M^{+\bullet}$), 315(74), 297(20), 216(100), 167(71), 139(41), 121(13), 93(21), 67(40).

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