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Stereochemical Course of the [4+2] Cycloaddition of 1-Methoxybuta-1,3-diene to *N*-Glyoxyloyl-(2*R*)-bornane-10,2-sultam. The Formal Synthesis of Compactin and Mevinolin

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Abstract: The chiral heterodienophile *N*-glyoxyloyl-(2*R*)-bornane-10,2-sultam **2**, readily prepared from (2*R*)-bornane-10,2-sultam **1**, was used in noncatalyzed atmospheric and high-pressure as well as in [Eu(fod)$_3$]-catalyzed [4+2] cycloadditions with 1-methoxybuta-1,3-diene **3**. All the [4+2] cycloadditions studied led to diastereoisomeric mixtures of 6-substituted derivatives of 2-methoxy-5,6-dihydro-2*H*-pyran **4-7**. The extent of asymmetric induction in these reactions was established by ^{1}H NMR analysis and the absolute configuration of the thermodynamically stable products **5** and **7** by X-ray analysis, and independently by chemical correlation. Stereochemical models for both noncatalyzed and [Eu(fod)$_3$]-promoted reactions are proposed. The [4+2] cycloadduct **5** was then effectively transformed into (4*R*)-hydroxy-(6*S*)-hydroxymethyltetrahydropyrone-2 **12**, a key synthon for the lactone moiety of compactin **10** and mevinolin **11**.

The Diels-Alder reaction of 1-alkoxybuta-1,3-dienes with alkyl glyoxylates leads to formation of 6-alkoxycarbonyl-2-alkoxy-5,6-dihydro-2*H*-pyrans in racemic form.[1] These cycloadducts are convenient substrates for stereoselective total syntheses of many monosaccharides,[2,3] and other natural products.[4,5] Attempts have been made to obtain these cycloadducts in optically active form by [4+2] cycloaddition of

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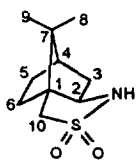
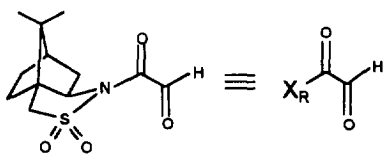
1-methoxybuta-1,3-diene **3** to enantiomerically pure esters of glyoxylic acid,[6] however, the diastereoselectivity of these reactions was low. Application of high-pressure techniques to the reaction of diene **3** with (*R*)-menthyl glyoxylate substantially improved the asymmetric induction,[7] nevertheless the degree of diastereoselection was still unsatisfactory. It appeared worthwhile to investigate the influence of the highly potent chiral auxiliary (2*R*)-bornane-10,2-sultam **1**, introduced and successfully applied by Oppolzer *et al.*,[8] on asymmetric induction in this type of the hetero-Diels-Alder reaction. Recently, we described an efficient method of the synthesis of *N*-glyoxyloyl-(2*R*)-bornane-10,2-sultam **2**,[9,10] and now its application to the hetero-Diels-Alder reaction with diene **3** is reported in detail.



1 X_RH



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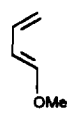
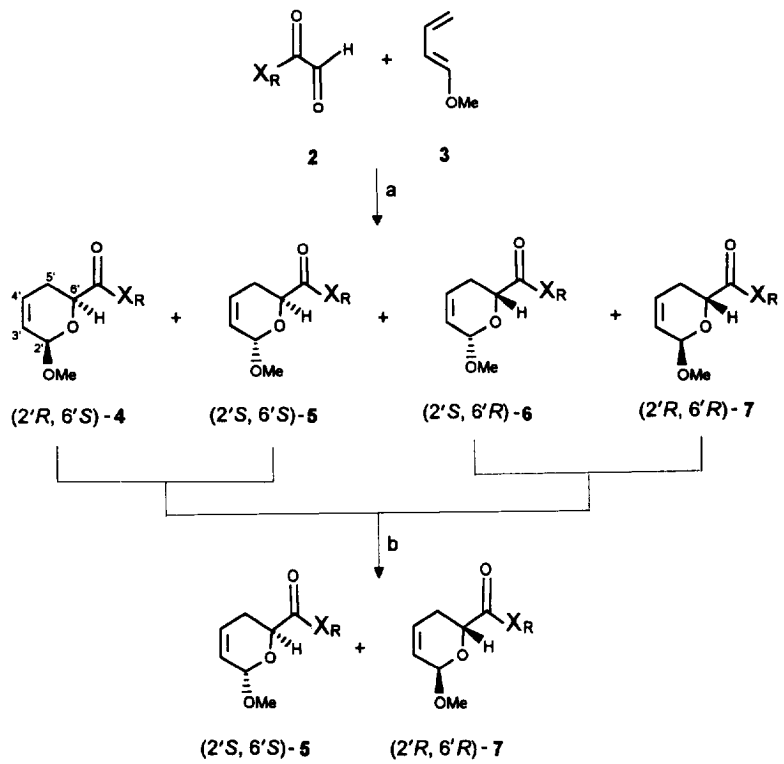


3

The [4+2] cycloaddition of diene **3** to chiral heterodienophile **2** gave rise to four chiral cycloadducts: two *cis*-diastereoisomers **4** and **6** by *endo*-addition, and two *trans*-diastereoisomers **5** and **7** by *exo*-addition. The ^{1}H NMR spectra of all diastereoisomers exhibited differences in chemical shifts (0.05-0.35 ppm) for the H-C(2') and H-C(6') signals, allowing precise integration and, hence, determination of the composition of the crude reaction mixture. The composition was independently confirmed by hydrogenation of the crude reaction mixture over the Adams catalyst, followed by the analogous ^{1}H NMR analysis. The crude reaction mixture was then subjected to acidic isomerization with pyridinium *p*-toluenesulfonate (PPTS),[11] which led to *trans*-diastereoisomers **5** and **7** (Scheme 1). The results of the [4+2] cycloaddition of diene **3** to heterodienophile **2**, carried out under various conditions, are presented in Table 1.

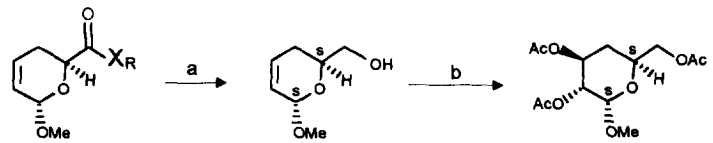
Several aspects of the data shown in Table 1 are noteworthy. The reaction carried out at ambient temperature and pressure afforded the diastereoisomeric cycloadducts in a good yield, but with rather low (46% d.e.) asymmetric induction (Entry 1). Therefore, we decided to enhance asymmetric induction by application of high-pressure techniques[7] and/or by Eu(fod)$_3$ catalysis.[12] The application of high-pressure methodology without catalyst (Entries 2-4) and with Eu(fod)$_3$[13] (Entries 5-7) failed to change substantially the yield and the stereoisomeric composition of the product. The best results in terms of both chemical yield (81%) and diastereoisomeric excess (88%) were obtained when the reaction was performed at ambient temperature and pressure in the presence of 2% Eu(fod)$_3$ for 1-3 h (Entries 9,10). Even better asymmetric induction was obtained at lower temperatures (Entries 11-15) albeit with a much

lower chemical yield. Entry 8 as compared with Entries 9 and 10 requires a few words of explanation. Lower asymmetric induction found for the reaction shown in Entry 8 resulted probably from the slightly lower stability of diastereoisomer **5** as compared with **7**; this fact causes the time-dependent change in the diastereoisomeric ratio.



Scheme 1. Reagents and reaction conditions: (a) 2% $Eu(fod)_3$ or without catalyst, CH_2Cl_2, 1 atm or ΔP, 20°C, 20 h; (b) PPTS, MeOH, RT, 15 h.

After the determination of the extent of asymmetric induction, we studied its direction by X-ray analysis as well as by chemical correlation. A mixture of compounds **5** and **7**, obtained from acidic isomerization of a crude mixture of [4+2] cycloadducts **4**, **5**, **6**, and **7** (Scheme 1), was readily separated by column chromatography into pure, crystalline, single diastereoisomers. The major diastereoisomer **5** was chemically correlated with compound **8** whose absolute configuration is known from an earlier correlation[1] with the natural sugar derivative **9** (Scheme 2).



(2'*S*, 6'*S*)-**5** **8** **9**

Scheme 2. Reagents and reaction conditions: (a) $LiAlH_4$, Et_2O, 0°C→RT, 2 h; (b) Ref. 1.

Table 1. The asymmetric [4+2] cycloaddition of diene **3** to heterodienophile **2**[a]

Entry	Pressure	Temp.	Time	Catalyst	Yield[b]	Content of diastereoisomers				Asymmetric induction
	[atm]	[°C]	[h]		[%]	**4**	**5**	**6**	**7**	(**4**+**5**) : (**6**+**7**)
1	1	20	20	none	73	44	29	14	13	73 : 27
2	8000	20	20	none	75	42	27	16	15	69 : 31
3	10000	20	20	none	76	43	28	15	14	71 : 29
4	12000	20	20	none	80	43	29	14	14	72 : 28
5	8000	20	20	2%Eu(fod)$_3$	80	30	44	8	18	74 : 26
6	10000	20	20	2%Eu(fod)$_3$	80	30	45	7	18	75 : 25
7	12000	20	20	2%Eu(fod)$_3$	83	30	47	6	17	77 : 23
8	1	20	20	2%Eu(fod)$_3$	81	8	81	2	9	89 : 11
9	1	20	3	2%Eu(fod)$_3$	81	5	89	1	5	94 : 6
10	1	20	1	2%Eu(fod)$_3$	81	5	89	1	5	94 : 6
11	1	-15	16	2%Eu(fod)$_3$	47	5	91	4[c]		96 : 4
12	1	-20	16	2%Eu(fod)$_3$	35	~4	92	<4[c]		>96 : 4
13	1	-20	32	2%Eu(fod)$_3$	46	~4	92	<4[c]		>96 : 4
14	1	-30	32	2%Eu(fod)$_3$	32	~4	92	<4[c]		>96 : 4
15	1	-78	75	2%Eu(fod)$_3$	36	~3	93	<4[c]		>96 : 4

[a] All the reactions were carried out in CH_2Cl_2 as a solvent.
[b] Isolated yields.
[c] A ratio (**4** + **5**) : (**6** + **7**) not sufficient to enable a precise ^1H NMR analysis.

Independently, the absolute configurations of both thermodynamically stable *trans*-diastereoisomers **5** and **7** were established using X-ray analysis. The results are presented in Figure 1 for compound **5**, and in Figure 2 for compound **7**.

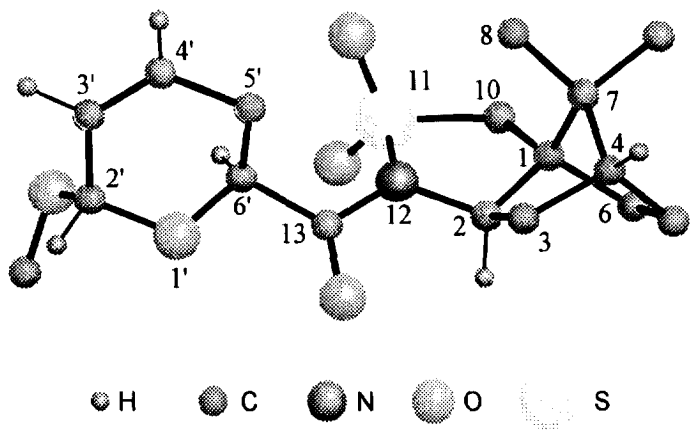


Figure 1. Molecular structure of compound (2'*S*,6'*S*)-**5**.

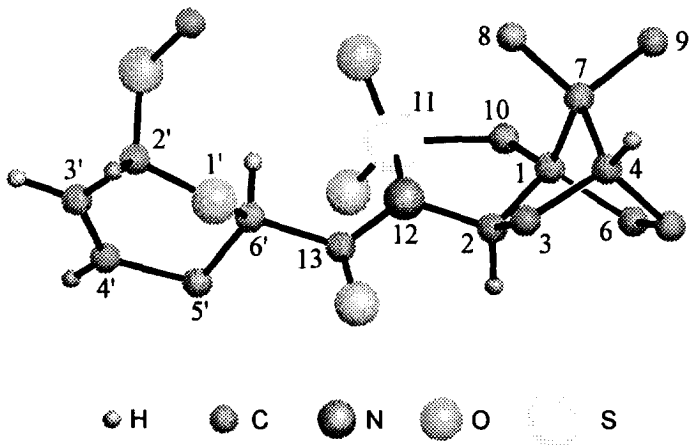
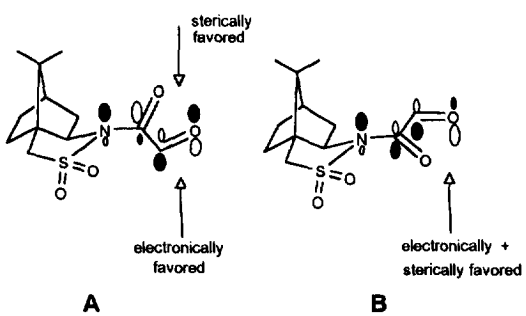


Figure 2. Molecular structure of compound (2'*R*,6'*R*)-**7**.

Rationalization of our results obtained for the noncatalyzed [4+2] cycloaddition may be based on two concepts: 1) the sterically controlled approach of a diene to the thermodynamically more stable SO_2/CO *anti*-periplanar, CO/CHO s-*cis* planar conformer A, as proposed by Oppolzer *et al.*,[8,15] and by Curran *et al.*,[16] for *N*-acryloyl- and *N*-crotonoyl-(2*R*)-bornane-10,2-sultam, and 2) the high reactivity of the less stable SO_2/CO *syn*-periplanar, CO/CHO s-*cis* planar conformer B (Scheme 3), reinforced by the cooperative stereoelectronic effect, as recently formulated by one of us.[17,18]



Scheme 3. The stereochemical models (LUMO level) for asymmetric induction in the reaction of heterodienophile **2** with diene **3**.

As suggested by X-ray analysis of *N*-acryloyl- and *N*-crotonoyl-(2*R*)-bornane-10,2-sultam,[8,15,16] for *N*-glyoxyloyl-(2*R*)-bornane-10,2-sultam **2** the more stable conformer A should be preferred over conformer B due to electrostatic and/or dipole-dipole repulsion between the sultam oxygen and the glyoxyloyl

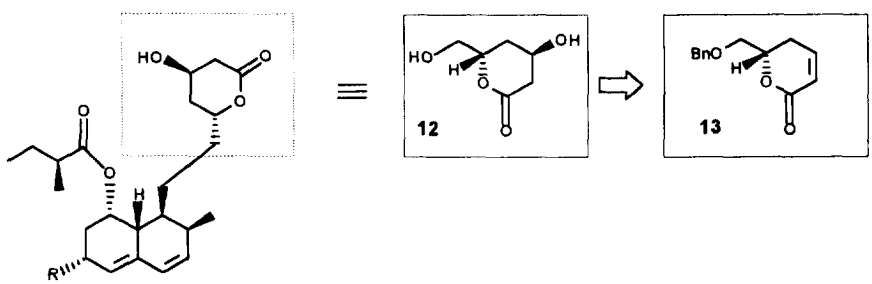
moiety.[19] It is also noteworthy that under high-pressure conditions, the CO/CHO s-*cis* conformation of the chiral glyoxylates is favored.[7,20] Therefore, the approach of a diene to the dienophile **2** should occur from the top side of the bornane skeleton, as already observed for noncatalyzed reactions of cyclopentadiene with *N*-acryloyl-,[15,21] *N*-crotonoyl-,[15,21] *N*-acylnitroso-,[22,23] and *N,N'*-fumaroyl-di-(2*R*)-bornane-10,2-sultam.[24] This fact has been recently rationalized by Kim and Curran[25] as the result of a *cis*-1,4 sterical congestion due to the α-oxygen atom of the sultam in analogy with 2,5-dimethylpyrrolidine.

Although initially invoked,[15,16,26] the fact that π-facial selectivity in the reaction of *N*-acyl-(2*R*)-bornane-10,2-sultam seemed to be independent of the electronic nature of the attacking reagent,[27] then led both Curran and Oppolzer to suspect that pyramidalization of the sultam nitrogen atom has no substantial stereoelectronical influence on the π-facial selectivity of the reactive double bond which is not directly branched to the sultam nitrogen atom.[25] In contrast, recent calculations at the semiempirical PM3 and *ab initio* STO3-21G level of theory,[17,18] suggest that among the conformations of low energy, the conformer B is the most reactive species in term of LUMO level and atomic coefficients.[28,29] This conformer thus could participate to the stereoselectivity outcome of the Diels-Alder reaction by kinetically driving, at least partially, thermodynamic equilibrium on its side. Furthemore, the N, (CO), C_α, and O atomic coefficients of the LUMO are nonequivalent with respect to both $C_{\alpha\text{-re}}$ and $C_{\alpha\text{-si}}$ faces, favoring, independently of the conformation, the attack on the opposite face to the nitrogen lone pair. This stereoelectronic effect is thus mismatching the steric effect in the conformer A, while being addtitive in conformer B, reinforcing its higher reactivity. The stereoelectronic effect is certainly depending on the electronic conjugation of the π system, which is reflected in part by the CO/CHO dihedral or "twisting" angle.[30] The conformational equilibrium may even be more complicated in view of, as recently proposed by Pindur *et al.*,[31] reactive SO_2/CO *anti*-periplanar, CO/CH=CH_2 s-*trans* planar conformation which cannot be excluded in our case,[9] due to the sterically less demanding reactive HC=O double bond as compared with the entropically more favored HC=CH_2 double bond. It is also noteworthy that the diastereoselectivity observed in our case reflects partially the selectivity of the *endo*-attack,[32] and thus it may also explain the moderate diastereoselectivity observed for the noncatalyzed reaction (Table 1, Entry 1).

In the case of *N*-crotonoyl-(2*R*)-bornane-10,2-sultam, addition of a strong Lewis acid such as $TiCl_4$ results in chelation of the carbonyl oxygen atom and the ß-oxygen atom of the sultam. This was proved by IR[8] and X-ray analysis[33] of the 1:1 complex. In that conformation, the reactive HC=$CHCH_3$ double bond is kept away from the α-oxygen atom of the sultam, and the "bottom attack" results from the steric repulsion of the bornane carbon skeleton, as initially postulated by Oppolzer[8] and Curran.[25] In contrast, the IR analysis of the 1:1 $TiCl_4$/compound **2** complex shows chelation of both carbonyl groups, as demonstrated by the hypsochromic shifts of both asymmetric and symmetric SO_2 stretchings

(1345→1375 and 1140→1155 cm^{-1}, respectively), and by the bathochromic shift of both CO strechings (1702→1580 cm^{-1}). Furthermore, addition of a weak Lewis acid such as $Eu(fod)_3$ to *N*-crotonoyl-(2*R*)-bornane-10,2-sultam causes only the simple complexation to the carbonyl group being in the *s-cis* conformation with respect to the reactive double bond.[15,21] The *s-cis* conformation is also postulated for the *N*-glyoxyloyl-(2*R*)-bornane-10,2-sultam (**2**) complexed with $Eu(fod)_3$, involving the same transition states and rationalization as postulated for the noncatalyzed reaction.

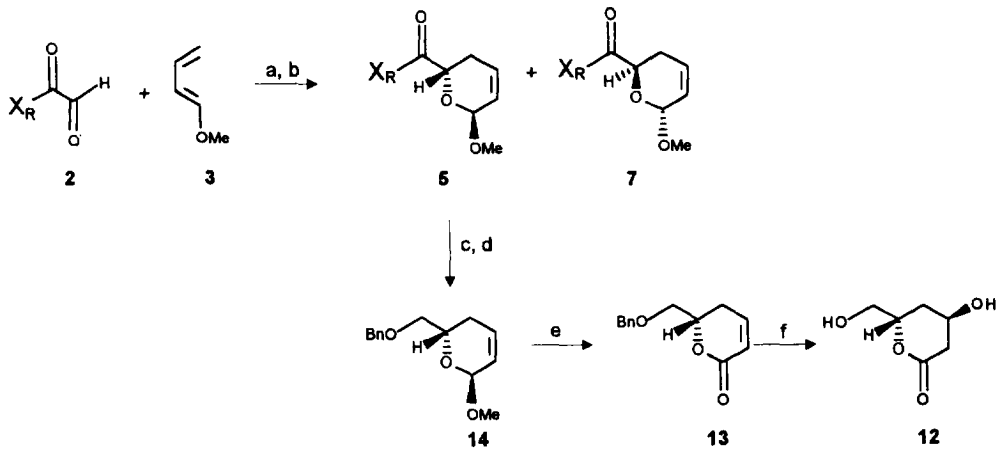
The next step of this work was the application of the above-presented results to the stereocontrolled synthesis of (4*R*)-hydroxy-(6*S*)-hydroxymethyltetrahydropyrone-2 **12**, a key intermediate for the lactone portion of compactin **10** and mevinolin **11**.[36] Compactin and mevinolin have been shown to reduce serum cholesterol levels and thus provide potential tools for the mitigation of arteriosclerosis.[37] In recent years these compounds have elicited much synthetic interest.[38] The (4*R*,6*R*)-lactone moiety of compactin and mevinolin is crucial for their biological activity.[39] Despite its simple structure, the synthesis of the (4*R*,6*R*)-tetrahydro-2-pyrone ring has proved to be challenging.[40-42] Most earlier syntheses suffered from low overall yields, a large number of steps, and a low stereoselectivity.[38]



10 R = H
11 R = Me

Our approach to this synthesis, according to the simple retrosynthetic analysis (**12**⇨**13**⇨**8**⇨**5**), is based on the highly stereocontrolled [4+2] cycloaddition of diene **3** to heterodienophile **2**, affording compound **5**[9] as the major diasteroisomer. Further reduction of **5** to compound **8**, followed by benzylation and anomeric oxidation should give a direct route to the desired product **12**.

We applied the $Eu(fod)_3$-catalysed [4+2] cycloaddition of **3** to **2**, carried out in methylene chloride under ambient conditions, followed by acidic isomerization and chromatographic purification (Scheme 4).



Scheme 4. Reagents and reaction conditions: (a) 2% $Eu(fod)_3$, CH_2Cl_2, 20°C, 3 h; (b) PPTS, MeOH, RT, 15 h; (c) LAH, THF, 0°C→RT, 30 min; (d) NaH, BnBr, 0°C→RT, 2 h; (e) 30% H_2O_2, MoO_3 (cat.), THF, RT, 1 h; Ac_2O, pyridine, RT, 10 h; (f)[12] 30% H_2O_2, 6*M* NaOH, MeOH; $(PhSe)_2$, $NaBH_4$, AcOH, Pr^iOH; H_2, $Pd(OH)_2$, AcOEt.

Reaction of compound **5** with lithium aluminum hydride (LAH), followed by benzylation of the resulting alcohol,[43] afforded in 50% overall yield the benzyl ether **14** which was subjected to anomeric oxidation with 30% H_2O_2 in the presence of catalytic amount of molybdenum trioxide.[44,45] Treatment of the resulting hydroperoxide with acetic anhydride and pyridine afforded the known[42] α,ß-unsaturated δ-lactone **13**, which was identical in all respects ($[\alpha]_D$, spectral data) with the authentic material. Compound **13** was finally transformed into the title pyrone **12** according to the known procedure given by Takano *et al.*[42]

The present synthesis of (4*R*)-hydroxy-(6*S*)-hydroxymethyltetrahydropyrone-2 **12** exemplifies the usefulness of the *N*-glyoxyloyl-(2*R*)-bornane-10,2-sultam **2** as an effective starting material in syntheses of various natural products *via* asymmetric Diels-Alder reactions. Moreover, this synthesis is an interesting practical alternative to the known approaches,[40-42] as it could be treated as the formal synthesis of compactin **10** and mevinolin **11**.

The present results open a convenient and efficient route to optically pure 2-alkoxy-5,6-dihydro-2*H*-pyrans, *eo ipso* to the synthesis of enentiomerically pure sugars and related natural products from noncarbohydrate precursors.

EXPERIMENTAL

General. Melting points were determined using a Kofler hot stage apparatus and are uncorrected. Rotations were recorded using a JASCO DIP-360 polarimeter with a thermally jacketed 10 cm cell. IR spectra were obtained on a Perkin-Elmer 1640 FTIR spectrophotometer in KBr pellets. ^{1}H NMR spectra were recorded using a Bruker AM 500 spectrometer and ^{13}C NMR spectra were recorded with DEPT editing as necessary, using also a Bruker AM 500 spectrometer. All chemical shifts are quoted in parts per milion relative to tetramethylsilane (δ, 0.00 ppm), and coupling constants (J) are measured in Hertz. Mass spectra were recorded on an AMD-604 Intectra instrument using the electron impact (EI) technique. Single-crystal X-ray diffraction analysis was performed on a Syntex $P2_1$ diffractometer. Flash column chromatography was undertaken according to Still *et al.*[34] on silica gel (Kieselgel-60, Merck, 200-400 mesh). 1-Methoxybuta-1,3-diene **3** was prepared according to the literature procedure,[35] and *N*-glyoxyloyl-(2*R*)-bornane-10,2-sultam **2** was obtained according to our own methodology.[10]

Preparation of (2'*S*)-methoxy-(6'*S*)-[(2*R*)-bornane-10,2-sultam]-carbonyl-5',6'-dihydro-2*H*-pyran **5** and (2'*R*)-methoxy-(6'*R*)-[(2*R*)-bornane-10,2-sultam]-carbonyl-5',6'-dihydro-2*H*-pyran **7**. A solution of diene **3** (4 mL, 40 mmol), heterodienophile **2** (2.0 g, 7.4 mmol), and $Eu(fod)_3$ (0.2 g) in CH_2Cl_2 (80 mL) was stirred at 20°C over a period of 3 h. The reaction mixture was filtered through a short silica gel pad, then the filtrate was evaporated to dryness and the oily residue was dissolved in MeOH (100 mL). To this solution PPTS (0.25 g, 1 mmol) was added. The *cis-trans* isomerization was carried out at room temperature over a period of 15 h, then solid $NaHCO_3$ (0.09 g, 1.1 mmol) was added, and the mixture was stirred over a period of 1 h. The solvent was evaporated and the residue was treated with Et_2O (10 mL). The precipitated inorganic salts were filtered off and the crude mixture was purified by flash chromatography (hexanes-ethyl acetate, 9:1) to afford the crystalline analytically pure product **5** (1.99 g) and its crystalline diastereoisomer **7** (0.13 g) (94:6, total yield 81%).

Diastereoisomer **5**: mp 215-217°C (from *n*-hexane-ethyl acetate); $[\alpha]_D^{20}$=-113.4 (*c* 1.2, $CHCl_3$); ν_{max} (KBr)/cm^{-1} 3013, 2956, 2883, 1703, 1456, 1402, 1325, 1288, 1238, 1195, 1137, 1051, 969, 905, 771, 721; δ_H (500 MHz; $CDCl_3$) 6.02-5.96(m, 1H), 5.80-5.75(m, 1H), 5.10(dd, J_1=11.3, J_2=3.7, 1H), 4.80(m, 1H), 3.97(dd, J_1=7.8, J_2=4.8, 1H), 3.48(ABq, J=13.7, 2H), 3.44(s, 3H), 2.44-3.97(m, 1H), 2.31-2.22(m, 1H), 2.13(dd, J_1=13.9, J_2=7.8, 1H), 2.05-1.99(m, 1H), 1.96-1.86(m, 3H), 1.47-1.34(m, 2H), 1.13(s, 3H), 0.98(s, 3H); δ_C(125 MHz; $CDCl_3$) 170.3, 127.1, 125.3, 95.5, 66.4, 64.9, 55.5, 53.0, 48.6, 47.8, 44.5, 38.1, 32.7, 28.2, 26.4, 20.7, 19.8; m/z (EIHR) calculated for $C_{16}H_{22}NO_4S$ $(M\text{-}OCH_3)^+$ 324.1269, found 324.1266.

Diastereoisomer **7**: mp 208-210°C (from *n*-hexane-ethyl acetate); $[\alpha]_D^{20}$=-100.9 (*c* 2.2, $CHCl_3$); ν_{max} (KBr)/cm^{-1} 3041, 2954, 2899, 2829, 1709, 1704, 1428, 1393, 1325, 1270, 1237, 1194, 1167, 1135, 1036, 967, 765, 712; δ_H (500 MHz; $CDCl_3$) 6.05-6.01(m, 1H), 5.75 (m, 1H), 5.03 (dd, J_1=11.0, J_2=3.5, 1H), 4.92(bs, 1H), 3.95(dd, J_1=7.8, J_2=4.9, 1H), 3.50(ABq, J=13.8, 2H), 3.44(s, 3H), 2.56-2.48(m, 1H), 2.25-2.14(m, 2H), 2.11(dd, J_1=13.9, J_2=7.8, 1H), 1.96-1.86(m, 3H), 1.45-1.33(m, 2H), 1.21(s, 3H), 0.99(s, 3H); δ_C (125 MHz; $CDCl_3$) 169.5, 127.2, 124.7, 95.6, 66.0, 65.1, 55.5, 53.0, 48.5, 47.6, 44.6, 38.2, 32.8, 26.2, 25.8, 20.7, 19.7; m/z (EIHR) calculated for $C_{17}H_{25}NO_5S$ $(M)^+$ 355.1453, found 355.1457; calculated for $C_{16}H_{22}NO_4S$ $(M\text{-}OCH_3)^+$ 324.1269, found 324.1266.

X-ray structure determination of diastereoisomers (2'*S*,6'*S*)-**5** and 2'*R*,6'*R*)-**7**. Crystal data and measurement conditions are given in Table 2. In the final steps of least-squares procedure all but methyl group H atoms were kept fixed at their calculated positions. The known configuration of the asymmetric centers of the sultam unit has been confirmed by the Flack parameter refinement.[46] The structure was solved by the SHELXS86[47] and refined with the SHELXL93[48] programs. The full data will be published separately.[49]

Table 2. Crystal data and measurement conditions for diastereoisomers (2'*S*,6'*S*)-**5** and (2'*R*,6'*R*)-**7**

	5	**7**
Formula	$C_{17}H_{25}NO_5S$	
Molecular weight	357.08	
Crystal system	orthorhombic	monoclinic
a [Å]	7.916(1)	11.637(2)
b [Å]	11.804(2)	11.737(2)
c [Å]	18.864(3)	13.637(2)
β [deg]	-	109.26(1)
V [Å^3]	1762.66	1758.34
Molecular multiplicity	*Z*=4	*Z*=4
Calculated density [g cm^{-3}]	1.34	1.34
Space group	$P2_12_12_1$	$P2_1$
Radiation (graphite monochromated)	Mo K_α	
Wavelenght [Å]	0.71069	
Linear absorption coeff. μ [cm^{-1}]	1.66	1.66
Number of electrons *F* (000)	760	760
Crystal size [mm]	0.25×0.30×0.45	0.25×0.45×0.50
Temperature [°C]	22±1	
Scan mode	$\theta/2\theta$	
Scan range (2θ) [deg]	0-54	
Number of collected data:		
total measured	2353	2720
unique [with $I > 2\sigma$]	1971	2434
R	0.0568	0.0437
R_w	0.0407	-
w	$1.037/\sigma^2_F$	-

Preparation of (2*S*)-methoxy-(6*S*)-benzyloxymethyl-5,6-dihydro-2*H*-pyran (**14**). To a solution of compound **5** (178 mg, 0.5 mmol) in dry THF (10 mL) was added at 0°C lithium aluminum hydride (20 mg, 0.5 mmol). After stirring at room temperature over a period of 30 min, the reaction mixture was treated with a saturated aqueous solution of sodium potassium tartrate (20 mL) and stirring was continued for additional 1.5 h. The post-reaction mixture was transferred into a separatory funnel and the aqueous layer was extracted with Et_2O (3x20 mL). The organic extracts were combined, dried ($MgSO_4$), and evaporated in vacuo. After removal of compound **1**, the crude alcohol **8**[43] was dissolved in dry THF (10 mL), the solution was cooled to 0°C, NaH (25 mg, 0.52 mmol) and BnBr (65 μL, 0.55 mmol) were added. The reaction mixture was stirred at room temperature over a period of 2 h, then Et_3N (140 μL, 1 mmol) was added and the mixture was stirred for additional 15 min. The post-reaction mixture was diluted with Et_2O (50 mL), washed with water (3x20 mL), brine (20 mL), and dried ($MgSO_4$). After evaporation in vacuo, the residue was subjected to flash chromatography (hexanes-EtOAc, 7:3) to afford the product **14** (58.5 mg, 50%) as an oil $[\alpha]_D^{20}$=-15.6 (*c* 0.6, $CHCl_3$); ν_{max} (film)/cm^{-1} 3040-2860, 1315, 1210, 1110; δ_H (200 MHz, $CDCl_3$) 7.38-7.28 (m, 5H), 6.02-5.95(m, 1H), 5.72 (ddd, J_1=4.1, J_2=2.6, J_3=1.4, 1H), 4.82 (bs, 1H), 4.60 (ABq, J_1=4.1, J_2=2.6, 2H), 4.23 (m, 1H), 3.75-3.66 (m, 2H), 3.38 (s, 3H), 2.25-2.15 (m, 1H), 1.95-1.82 (m, 1H).

Preparation of (6*S*)-benzyloxymethyl-5,6-dihydro-2*H*-pyrone-2 **13**. To a solution of compound **14** (68 mg, 0.29 mmol) in dry THF (0.5mL) 30% H_2O_2 (3 mL) and a catalytic amount of MoO_3 were added, and the mixture was stirred at room temperature over a period of 1 h. The reaction mixture was diluted with water (30 mL) and extracted with CH_2Cl_2 (3x20 mL). The combined extracts were washed with water (2x20 mL), brine (20 mL), dried ($MgSO_4$), and the solvent was evaporated in vacuo. The resulting crude hydroperoxide was dissolved in pyridine (1.5 mL), Ac_2O (150 μL, 1.5 mmol) was added, and the mixture was stirred at room temperature over a period of 10 h. Then solvents were evaporated in vacuo, the residue was dissolved in toluene (2x25mL) and evaporated. Flash chromatography (hexanes-EtOAc, 7:3) of the residue afforded the lactone **13** (48 mg, 75%) as an oil. $[\alpha]_D^{20}$=-115.8 (*c* 1.2, $CHCl_3$); Lit[42] $[\alpha]_D^{20}$=-115.0 (*c* 1, $CHCl_3$); ν_{max} (film)/cm^{-1} 3060-2860, 1730, 1510, 1220; δ_H (500 MHz, $CDCl_3$) 7.39-7.28 (m, 5H), 6.90 (ddd, J_1=9.8, J_2=6.0, J_3=2.5, 1H), 6.02 (ddd, J_1=9.8, J_2=2.7, J_3=1.0, 1H), 4.64-4.55 (m, 3H), 3.37-3.66 (m, 2H), 2.61-2.53 (m, 1H), 2.56 (1/2ABq ddd, J_1=18.5, J_2=11.6, J_3=J_4 =2.6, 1H), 2.40 (1/2ABq ddd, J_1=18.5, J_2=5.8, J_3= 4.2, J_4=1.0, 1H) ; δ_C (125 MHz, $CDCl_3$) 163.7, 144.8, 137.7, 128.5, 127.9, 127.7, 121.2,

76.6, 73.7, 70.8, 26.2; m/z (EIHR) calculated for $C_{13}H_{14}O_3$ $(M)^+$ 218.0943, found 218.0923; calculated for $C_5H_5O_2$ $(M\text{-}CH_2OBn)^+$ 97.0289, found 97.02889.

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