Diastereoselective Zwitterionic Aza-Claisen Rearrangement: The Synthesis of Bicyclic Tetrahydrofurans and a Total Synthesis of (+)-Dihydrocanadensolide

Udo Nubbemeyer

Institut für Organische Chemie, Freie Universität Berlin, Takustrasse 3, D-14195 Berlin, Germany

Received January 4, 1996[⊗]

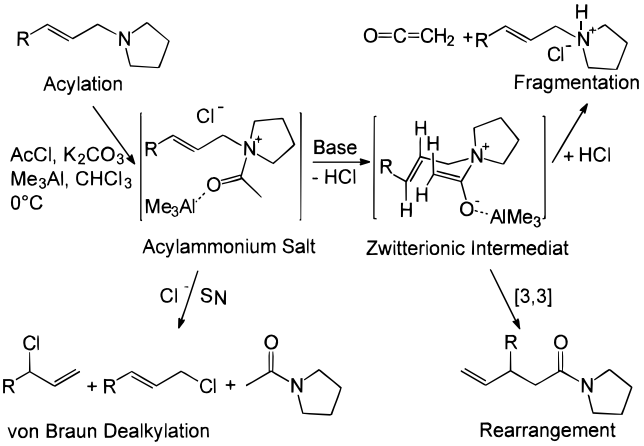
The zwitterionic Claisen rearrangement of optically-active *N*-allyl pyrrolidines and various acid chlorides proceeds with high simple diastereoselection (internal asymmetric induction) and high 1,2-asymmetric induction, generating a new C−C bond adjacent to a chiral C−O function. The resulting γ,δ-unsaturated amides were cyclized to the corresponding optically active γ-butyrolactones, which are useful intermediates in natural product synthesis. On one hand, a diastereoselective iodocyclization of several lactones led to tetrahydrofurans with a substitution pattern representing a key intermediate of an oxa-prostaglandin synthesis. On the other, a one-pot procedure of a Swern oxidation and consecutive Grignard reaction of one γ-lactone allowed a diastereoselective chain elongation. The final oxidation/cyclization sequence completed a highly efficient synthesis of the (+)-dihydrocanadensolide or its C-3 epimer, respectively.

Introduction

The influence of a chiral center outside the pericyclic system on the stereochemical result of the Claisen rearrangement has been widely investigated. In most cases the degree of 1,2-asymmetric induction (relative asymmetric induction) is low for the formation of a new C−C bond in α-position to a chiral C−O bond.[1] Especially in acyclic substrates bearing glyceraldehyde or related fragments,[2] high diastereoselectivities are more of an exception.[3]

Diastereoselective ketene Claisen rearrangements of allyl thioethers are well known,[4] but the scope of the reaction is restricted to activated ketenes like chloro-, chloroalkyl-, and dichloroketene.[5] Aza-ketene Claisen reactions involving *in situ* generated ketenes (especially dichloroketene) suffer from the same disadvantages.[6] All rearrangements are accompanied by varying amounts of tarry side products.[6a] In contrast, treatment of *N*-allylpyrrolidines with acid chlorides in presence of trimethylaluminum in a two-phase system led to the corresponding γ,δ-unsaturated amides in high yields (zwitterionic variant, for a postulated reaction path see Scheme 1).[7,8] Low 1,2-asymmetric induction (generation of a new C−C bond adjacent to a chiral C−O function) was observed when reacting acetyl chloride with the allylamines, but the rearrangement with propionyl chloride allowed the generation of two new chiral centers in one step with a high diastereomeric excess.[8]

Scheme 1



The major competing reaction observed is a von Braun type dealkylation process[6b,9] involving a nucleophilic attack of a chloride ion on an intermediate acyl ammonium salt.[8] The von Braun type reaction path predominated whenever α,α-disubstituted acid chlorides (e.g., dichloracetyl chloride) were used.

[⊗] Abstract published in *Advance ACS Abstracts,* May 1, 1996.

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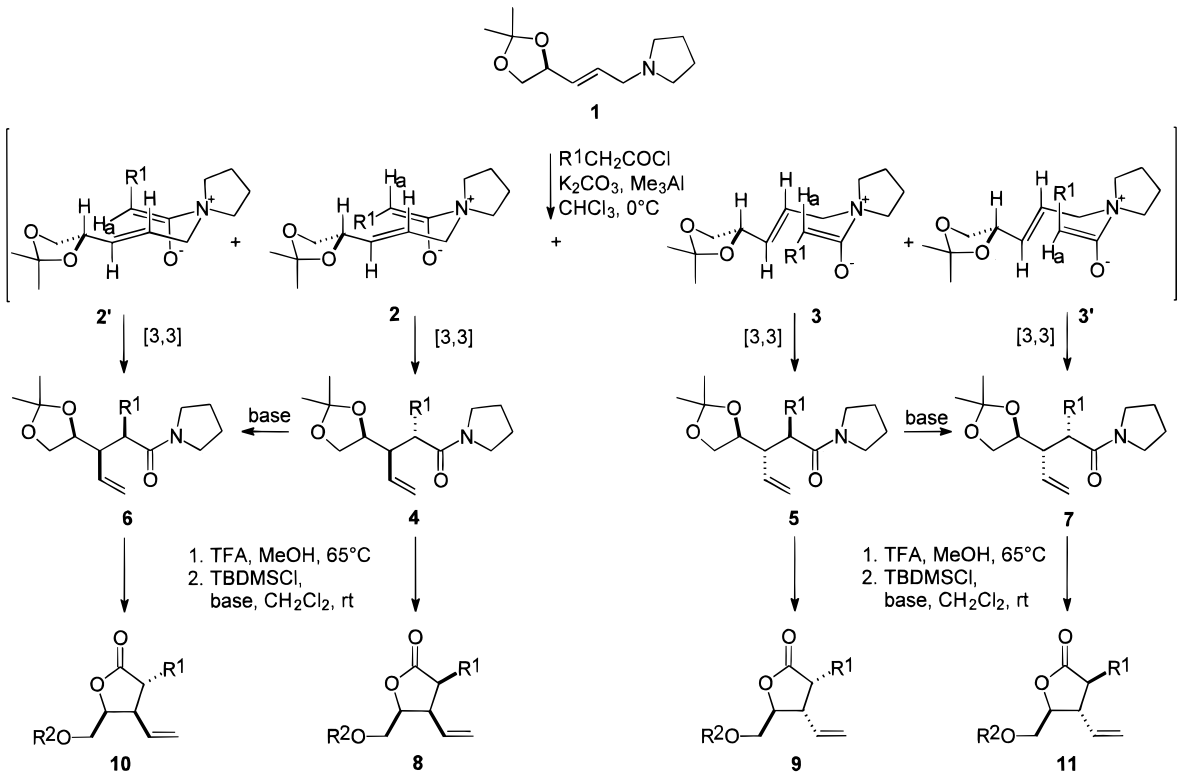
S0022-3263(96)00046-1 CCC: $12.00

Table 1. Results of the Zwitterionic Aza-Claisen Rearrangement

			ratio				yield [%]				
entry	R^1	yield [%]	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	ref
a	H	82	60	40	–	–	92[b]	90[b]	–	–	5
b	CH_3	77	90	10	<1	<1	85[a]	89[b]	–	–	5
c	CH_2CH_2Cl	74	70	<1	30	<1	92[b]	–	90[b]	–	
d	$CH(CH_3)_2$	45	>97	<1	<1	<1	91[b]	–	–	–	
e	$CH{=}CH_2$	62	>97	<1	<1	<1	84[a]	–	–	–	
f	$CH{=}CHCH{=}CH_2$	60	<1	<1	>97	<1	–	–	85[a]	–	
g	C_6H_5	52	<1	<1	>97	<1	–	–	92[b]	–	
h	Cl	82	96	2	<1	<1	95[a] 88[b]	–	–	–	
i	$OCH_2C_6H_5$	83	87	8.7	<1	4.3	92[a]	59[b]	–	29[b]	

[a] R^2 = H. [b] R^2 = TBDMS.

Scheme 2



Results and Discussion

In the first part of this paper, the scope and the limitations of the zwitterionic aza-Claisen rearrangement of the acyclic allylamine **1** is reported. The allylamine **1** was generated in six steps starting from D-mannitol, or in three steps from (*S*)-*E*-4,5-(isopropylidenedioxy)-2-pentenoic acid ethyl ester.[8]

Diastereoselective Aza-Claisen Rearrangement. The *N*-allylpyrrolidine **1** was treated with several types of acid chlorides, as described in Table 1 and Scheme 2. All isolated amides **4**−**7** were cyclized to the corresponding γ-butyrolactones **8**−**11** in MeOH/TFA.[10] In several attempts, the remaining hydroxyl function was protected as the *tert*-butyldimethylsilyl ether.[11] The relative stereochemistry of each compound from **8** to **11** was unequivocally proved *via* NOEDS (nuclear Overhouser effect difference spectroscopy) analysis.

In the first series, allylamine **1** was acylated with a range of alkanoyl chlorides to give rearranged products (entries a−d). The corresponding γ,δ-unsaturated amides could be isolated in high yields in the case of linear chains (entries a−c). While the adduct with acetyl chloride (entry a) rearranged with modest 1,2 asymmetric induction, propionyl chloride (entry b) gave a mixture of amides **4b** and **5b** in a 9:1 ratio.[8] The reaction of the 4-chlorobutyric acid chloride (entry c) did not produce the *anti* amide **5c** or **7c** (100% 1,2-asymmetric induction), but the simple diastereoselection was found to be nonuniform. Presumably, the product **4c** had partially epimerized during the extended reaction time. Furthermore, 3-methylbutyric acid chloride (branched side chain, entry d) could be used to generate the amide **4d** exclusively, but only a modest yield (45%) was obtained, despite a very long reaction time (about 3−4 weeks), and a significant amount of von Braun type side products was formed. 2-Methylpropionic acid chloride did not give any rearrangement product.

In the second series, rearrangements with unsaturated acid chlorides were investigated (entries e−g). In all attempts, only a single diastereomer could be detected. The reaction of allylamine **1** with 2-butenoic- or 2,4-hexadienoic acid chloride formed the corresponding un-

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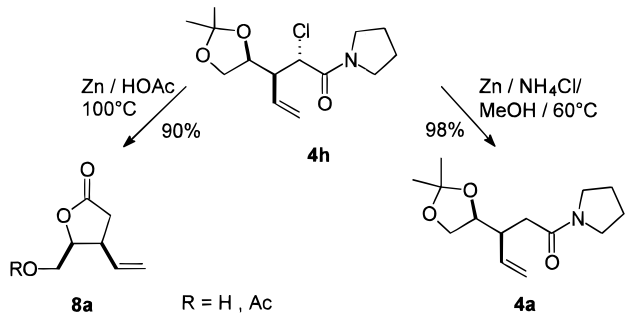
Scheme 3



saturated amides **4e** and **6f** in 62% and 60% yield, respectively. Compared with the saturated acid chlorides of series 1, the amount of von Braun type products increased. It should be pointed out that the β,γ-double bonds of the products did not isomerize, and the α,β-unsaturated amide was not found. After the cyclization to the γ-lactones, only the 3,4-divinyl lactone **8e** contained a small amount (about 5%) of the conjugated olefinic system, which could be separated *via* preparative HPLC. It is noteworthy that the γ-lactones **8e** and **10f** were unstable and decomposed within one or two days. Phenylacetyl chloride slowly reacted with the allylamine **1** to form the α-phenylpyrrolidinamide **6g** exclusively in 52% yield. The very long reaction time (about 4 weeks) led to the formation of a high amount of von Braun type products.

The third series employed α-heteroatom-substituted acetyl chlorides in the rearrangement reaction with the allylamine **1** (entries h, i). Surprisingly, the reaction of chloroacetyl chloride proceeded with excellent induction. Simple diastereoselection generated the α-chloro amides **4h** and presumably **5h** (for which the relative stereochemistry of the minor diastereomer has not been determined) in a ratio of about 60:1 in 82% yield, even though the major product could undergo a facile α-epimerization. Furthermore, the cyclization and protection of the remaining hydroxyl function in the presence of pyridine formed the lactone **8h** exclusively, and the relative stereochemistry of all stereogenic carbon atoms was found to be *syn*! In contrast, the rearrangement of the allylamine with (benzyloxy)acetyl chloride led to the lowest 1,2-asymmetric induction of all the tested acid chlorides, and the amides **4i**, **5i**, and **7i** were isolated in a ratio of 20:2:1 and 83% yield. The minor diastereomers **5i** and **7i** were separated from the major product **4i** via HPLC. The separation of these components failed at this stage, but was achieved after cyclization and silylation to the lactones **9i** and **11i**. With dichloroacetyl chloride, only von Braun type products were obtained.[7,8]

The high diastereoselection achieved with the chloroacetyl chloride (entry h) provided an alternative to the unselective acetyl chloride rearrangement (entry a).[8] The dehalogenation of amide **4h** with Zn/NH_4Cl in refluxing MeOH[12] generated amide **4a** in nearly quantitative yield. The reduction with Zn in HOAc[5b] led to lactone **8a** in 82% yield and about 8.5% of the impure corresponding 5-acetoxymethyl lactone (Scheme 3).

Mechanistic Conclusions. The acyclic Claisen rearrangement is known to pass preferentially through a chairlike transition state[1,13] arranging the substituents in quasiequatorial positions. According to the observations of Evans, Myers, and Sonnet in their amide enolate

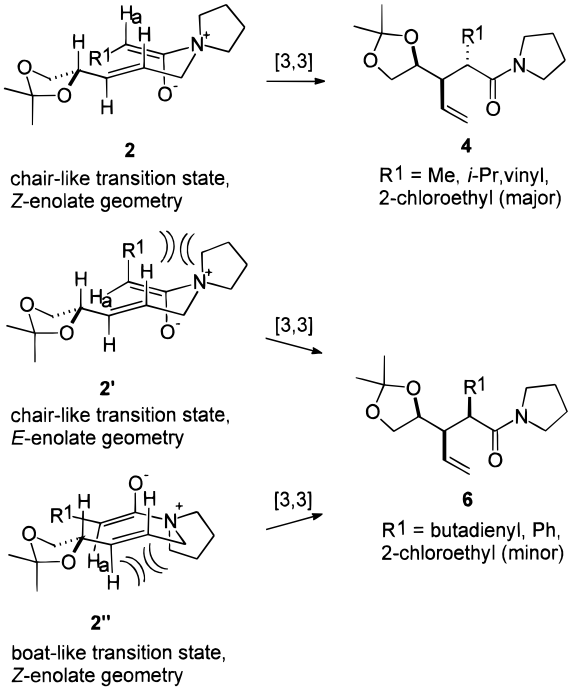


Figure 1. Chair- and boatlike intermediates of the rearrangement of allylamine **1** with carboxylic acid chlorides.

chemistry[14] and of Tsunoda in the rearrangement of amide enolates,[15] the deprotonation of an acyl ammonium salt should generate the *Z*-enolate structure **2** (Figure 1) or **3** because of steric (and 1,3-diaxial) repulsions. Obviously, the defined enolate geometry resulted in the high simple diastereoselection of the zwitterionic aza-Claisen rearrangement (Table 1, entries b−e, h, i). In contrast, the results of entries f and g were incompatible with these considerations.[16] A speculative quantitative epimerization under the basic reaction conditions would not serve as a satisfactory explanation in view of the results of entry c (R^1 = 2-chloroethyl, mixture of diasteromers), entry e (R^1 = vinyl), or entry h (R^1 = Cl). It seems reasonable that either the positions of H_a and R^1 are exchanged in the intermediate **2** (→ **2′**, *E*-enolate, Figure 1) or the reaction passes through the corresponding boatlike transition state **2″** (*Z*-enolate, eclipsed arrangement of the substituents, Figure 1). Steric arguments cannot be exclusively responsible for such different geometry (entry d: R^1 = isopropyl gave the expected relative stereochemistry). It appears more likely that electronic aspects of the enolate stabilization in the extensive π-system of the phenyl and the butadienyl substituents may be involved ("in plane arrangement" of the π-systems of enolate and substituent R^1). The

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mostly high simple diastereoselectivity (internal asymmetric induction) is comparable to those achieved with the well known Eschenmoser type rearrangements.[17]

In view of the model for the steric and electronic course of [3,3]-sigmatropic processes proposed by Kahn,[18] Houk,[19] and Felkin,[20] the reaction should preferentially pass through intermediate **2**, **2′** or **2″** leading to the observed 1,2-asymmetric induction (formation of the amides **8** or **10**). The generally high asymmetric induction with a range of acid chlorides represents the major advantage of this variant of the Claisen rearrangement.

In the second part of this paper, the γ,δ-unsaturated amides and the corresponding γ-lactones were investigated in further synthetic applications.

Iodocyclizations. In analogy to the high 1,2-asymmetric induction achieved during the Claisen rearrangement, the defined functionalization of the remaining double bond was investigated using iodocyclizations. Yoshida *et al.*[21] showed that acyclic 2-substituted and 2,3-disubstituted γ,δ-unsaturated *N*,*N*-dimethylamides of defined configuration underwent diastereoselective iodolactonization. The de values observed were ≥90% in accordance with high remote stereocontrol in a postulated five-membered transition state. In contrast, initial experiments starting from the 2,3-disubstituted pyrrolidine amide **4h** resulted in disappointing diastereoselectivity, despite the similar substitution pattern to that described by Yoshida (leading to high stereoselectivity). Presumably in this case, the favored transition state **13** generating the *syn*-lactone **15** was counteracted by the relative stereochemistry of the stereogenic dioxolane center. The mismatched configuration of **4h** resulted in unselective iodolactonization, with formation of a 54:46 mixture of the lactones **14** and **15**. The relative stereochemistry was determined *via* NOEDS analysis (Scheme 4).

Significantly higher stereoselectivity could be achieved by cyclization of the hydroxy lactones **8a** to **8i**. While after the cyclization of lactone **8a** two diastereomers **18a** and **19a** could be detected in a 5:1 ratio, the cyclizations of the lactones **8b** to **8i** generated single diastereomers **18b** to **18i** in high yields (Scheme 4). The relative stereochemistry was confirmed by NOEDS analysis. Obviously, the 3,4,5-*syn* substitution pattern of the lactones of type **8** favored a defined arrangement of the double bond in the iodonium intermediate **16** that resulted in a diastereoselective formation of the 2,3,4-trisubstituted tetrahydrofuran system. The substitution pattern is known from a synthesis of oxa-prostaglandins.[22] The lack of the *syn*-substituent at C-3 proved crucial and resulted in decreased stereoselection, as shown in the reaction of lactone **8a**.

Synthesis of the Dihydrocanadensolides 22 and 24. Dihydrocanadensolide **24** is a mold metabolite of *Penicillum canadense* with unknown biological activity, isolated by McCorkindale.[23] The correct relative stereochemistry was determined by Yoshikoshi[24] and a first

Scheme 4

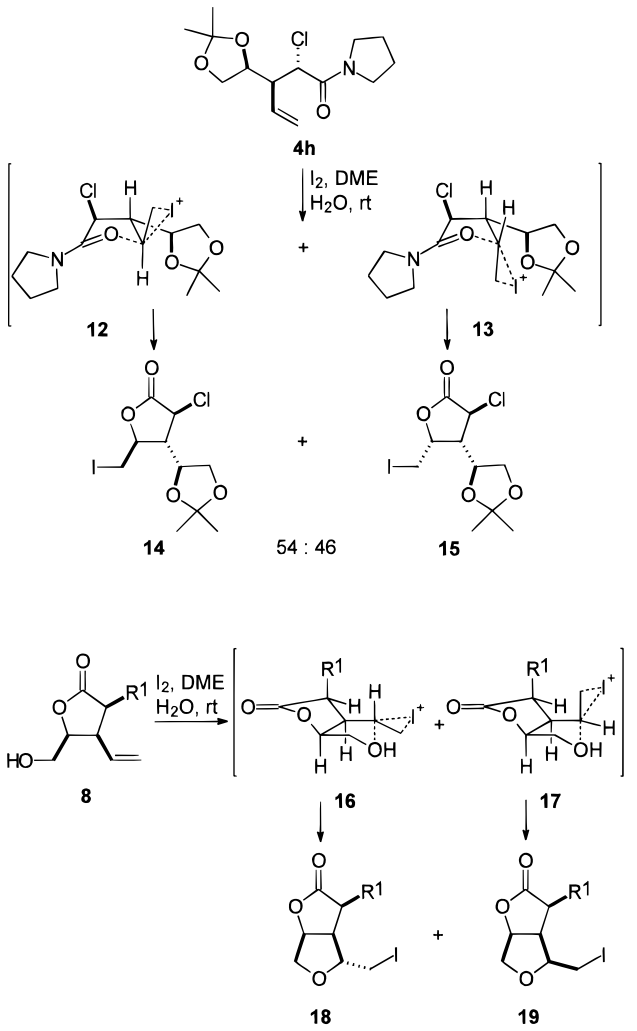

Table 2. Results of the Iodocyclization of Lactone 8

			ratio	
entry	R^1	yield [%]	**18**	**19**
a	H	87	84	16
b	CH_3	88	>98	<2
h	Cl	85	>98	<2
i	$OCH_2C_6H_5$	94	>98	<2

total synthesis was described by Mulzer.[25] The highly efficient diastereoselective generation of the γ-butyrolactone **8b** was used in a short synthesis of (+)-dihydrocanadensolide (**24**) and its C-3 epimer **22** (Scheme 5). The *n*-butyl side chain was introduced via a one-pot procedure of a Swern oxidation and Grignard addition following a procedure developed previously.[26] The fourth stereocenter was introduced according to the cyclic Cram model[27] generating predominantly the desired *syn* product **21** (ratio: **21**:**20** = 10:1) in 88% yield. The diastereomers could be separated *via* preparative HPLC or *via* flash column chromatography. The annulation of the second γ-lactone ring was achieved by a sequence of two oxidation steps:[26] After ozonolysis of the *syn*-lactone **21**

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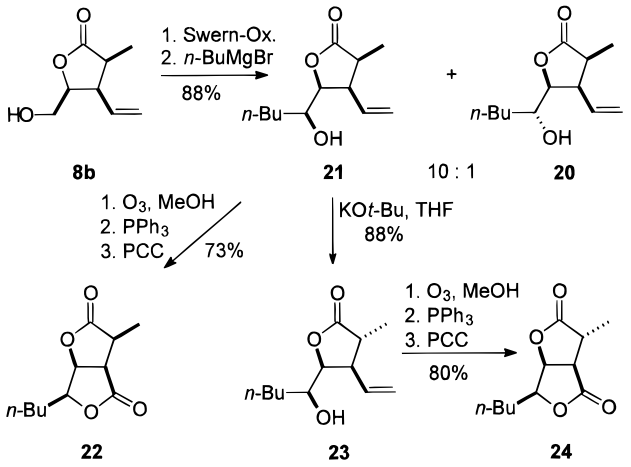
Scheme 5



followed by a reductive workup, the lactol generated *in situ* was transferred into a suspension of pyridinium chlorochromate. 3-*epi*-Dihydrocanadensolide (**22**) could be isolated in 73%. In preparation for synthesis of the (+)-dihydrocanadensolide (**24**), it was imperative to epimerize the 3-methyl group before generation of the bislactone structure. Otherwise, the bridgehead hydrogen of C-3a would be abstracted under the basic conditions, and the molecule would undergo a β-elimination to form a butenolide structure.[28] An epimerization of the 3-methyl substituent was successfullly carried out by treating the lactone **21** with 0.5 mol equiv of KO*t*Bu in THF,[29] and the diastereomeric lactone **23** was isolated in 88% yield. The final oxidation sequence as described for the 3-*epi* product allowed the generation of the (+)-dihydrocanadensolide (**24**) in 80% yield over two steps. All spectroscopic data and the melting point were identical with those published in the literature. In conclusion, the synthesis of the dihydrocanadesolide (**24**) with four asymmetric centers proceeded in 13 steps (10 isolated), starting from D-mannitol, in 12% yield overall. All new optically active carbon centers could be introduced with diastereoselections $\geq$9:1.

Conclusion

The zwitterionic Claisen rearrangement with allylamine **1** is characterized by its mild reaction conditions resulting in high diastereoselection rates with several substituted ketene analogs. The Eschenmoser type γ,δ-unsaturated amides were generated involving acid chlorides in the process.[17] A major advantage is that the difficult synthesis of the corresponding *N,N*-dialkylacylamide dialkylacetals and the high reaction temperatures of the original Eschenmoser rearrangement[17] can be avoided. In contrast to the most common acyclic Claisen rearrangements,[1,2] high 1,2-asymmetric inductions were achieved with a range of acid chlorides, and the disappointing selectivity of the acetyl chloride reaction was overcome by the chloroacetyl chloride-rearrangement/dehalogenation sequence. The high simple diastereoselectivity (internal asymmetric induction) originates from the defined enolate geometry in a hypothetical zwitterionic intermediate. The majority of entries generated a substitution pattern like in a Burke−Kallmerten[30] type rearrangement and assigned a preferentially quasiequatorial position of the substituent of the acid chloride in a chairlike conformation. An interpretation of the different behavior of 2,4-hexadienoic acid chloride and phenylacetyl chloride is still speculative. Further experiments concerning this problem are in progress.

First attempts at the iodolactonization of the γ,δ-unsaturated amide **4b** led to disappointing diastereoselection. After the cyclization of the amides to the corresponding γ-butyrolactones, the iodocyclizations proceeded with high diastereoselections in high yields indicating efficient remote stereocontrol *via* a five-membered transition state when *syn*-trisubstituted reactants were involved. The resulting tetrahydrofurans **18** (available in nine steps from mannitol, ca. 20% yield overall) are useful intermediates for natural product synthesis, e.g., the generation of the well known oxaprostaglandins[22] has been described *via* a bicyclic type **18a**.

Furthermore, an efficient and short ex-chiral pool synthesis of (+)-dihydrocanadensolide (**24**) has been described which improves the value of the zwitterionic aza-Claisen reaction for natural product synthesis. Two of the four chiral centers are formed in this key step with a high diastereoselection, one of which is built up in a stereoselective Grignard addition. Additionally, the primary generation of the 3,4,5-*syn* substituted γ-lactones allowed the efficient epimerization of the 3-position under basic conditions, resulting in the selective synthesis of a second substitution pattern of the γ-lactone system. The highly diastereoselective key steps of this synthesis recommend the method for further applications.

Experimental Section

For general experimental data see ref 26. The ^{1}H-NMR spectra of **6f**, **8c**, **8e**, **10c**, **14**, **18a**, **18b**, **18i** and the NOEDS analyses of **8e**, **14**, **18a**, **18b**, **18h**, **18i** were recorded on a Bruker AC 550 (500 MHz) spectrometer. Satisfactory analytical data (± 0.4% for C, H, N) are reported for all new compounds except **5h**, **5/7i**, **6f**, **10f** (HRMS data were included for these products).

(3*S*,4*S*) 3-Ethenyl-4,5-(isopropylidendioxy)pentanoic Acid Pyrrolidinamide (4a). The 2-chloro amide **4h** (0.3 g, 1.04 mmol) was dissolved in MeOH (30 mL), saturated with NH_4Cl. Then, Zn (powder, 0.62 g, 9.48 mmol) was added and the mixture was heated to reflux (65 °C) with stirring. After about 1 h, the reaction was found to be complete. After cooling the mixture to rt, H_2O (50 mL) was added and the mixture was extracted with CH_2Cl_2 (5 × 25 mL). The organic layers were dried ($MgSO_4$), and the solvent was removed to give pure amide **4a**: 159 mg (98%). For spectral data see ref 8.

Standard Procedure for the Zwitterionic Claisen Rearrangement. Under argon, dry K_2CO_3 (1.6 g, 11.6 mmol) was suspended in dry $CHCl_3$ (35 mL) and cooled to 0 °C. *N*-Allylpyrrolidine (5 mmol) and acid chloride (6 mmol) were added subsequently by means of a syringe. After about 30 min of stirring at 0 °C, a solution of Me_3Al (0.25 mL, 0.51 mmol, 2 M in toluene) was added *via* syringe. The mixture was stirred at 0 °C. After 24 h, a second volume of Me_3Al was injected. After 2 to 3 d, the reaction was stopped by quenching dropwise with saturated aqueous $NaHCO_3$ (5−10 mL) at 0 °C until the Al_2O_3/K_2CO_3 precipitated. Then, the organic layer was decanted, the solid residue was extracted with CH_2Cl_2 (5 × 20 mL), and the combined organic layers were dried ($MgSO_4$). The solvent was removed, and the crude mixture of diastereomeric amides and von Braun type products was purified by column chromatography. If necessary, diastereomers were separated *via* HPLC or column chromatography on silica gel.

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If the crude product contained more than 10% allylic amine (occurred in the majority of the experiments), the mixture was subjected to these reaction conditions for a second cycle.

(2*S*,3*R*,4*S*)-2-(2-Chloroethyl)-3-ethenyl-4,5-(isopropylidendioxy)pentanoic Acid Pyrrolidinamide (4c) and (2*R*,3*R*,4*S*)- 2-(2-Chloroethyl)-3-ethenyl-4,5-(isopropylidendioxy)pentanoic Acid Pyrrolidinamide (6c). Reaction with allylamine **1** (2.35 g, 11.12 mmol) following the standard procedure, reaction time: 6 d. Chromatography: EtOAc/hexanes 1:1, $R_f = 0.17$ (**4c**) and $R_f = 0.22$ (**6c**). Yield: 2.77 g (79%). Separation of the diastereomeric amides **4c** and **6c** (ratio: 7:3) *via* preparative HPLC: Eluent: 5% 2-propanol in hexanes. Major diastereomer amide **4c**: retention time 3.33 min, 1.94 g (55.3%). $[\alpha]^{23}_D$ −2.1 ($c = 0.9$ in $CHCl_3$): IR (KBr, film) 3076, 1634 (CO), 1444, 1380, 1370 cm^{-1}. MS (EI, 70 eV, 60 °C): *m/z* 315 (M^+), 300 ($M^+ - CH_3$), 280, 214, 175, 152, 126, 98, 83, 70. ^{1}H-NMR δ 1.34 (s, 3 H), 1.42 (s, 3 H), 1.90 (m, 4 H), 2.08 (m, 1 H), 2.24 (m, 1 H), 2.40 (dt, $J = 2.5$, 8.8 Hz, 1 H), 3.10 (dt, $J = 3.8$, 8.8 Hz, 1 H), 3.46 (m, 4 H), 3.64 (m, 3 H), 3.98(t, $J = 7$ Hz, 1 H), 4.36 (m, 1 H), 5.10 (d, br, $J = 17.5$ Hz, 1 H), 5.16 (d, br, $J = 10$ Hz, 1 H), 5.88 (td, $J = 10$, 17.5 Hz, 1 H). ^{13}C-NMR δ 24.1 (t), 24.9 (q), 25.8 (t), 25.9 (q), 32.5 (t), 42.7 (d), 43.2 (t), 45.4 (t), 46.7 (t), 48.5 (d), 66.9 (t), 73.9 (d), 108.7 (s), 118.7 (t), 134.0 (d), 171.7 (s). Anal. Calcd: C, 60.85; H, 8.3; N, 4.43. Found: C, 60.71; H, 8.15; N, 4.22. Minor diastereomer amide **6c**: retention time 2.91 min, 0.83 g (23.6%). $[\alpha]^{23}_D$ 31.9 ($c = 0.8$ in $CHCl_3$). IR (KBr, film) 3075, 1631 (CO), 1444, 1380, 1370 cm^{-1}. MS (EI, 70 eV, 60 °C): *m/z* 315 (M^+), 300 ($M^+ - CH_3$), 280, 257, 222, 215, 175, 152, 126, 101, 98, 71. ^{1}H-NMR δ 1.30 (s, 3 H), 1.40 (s, 3 H), 1.98 (m, 4 H), 2.40 (t, br, $J = 8$ Hz, 1 H), 2.54 (q, br, $J = 7.5$ Hz, 1 H), 3.08 (m, 1 H), 3.40 (dt, br, $J = 4.3$, 10 Hz, 1 H), 3.52 (t, br, $J = 6.3$ Hz, 2 H), 3.64 (m, 4 H), 3.92 (m, 2 H), 4.06 (t, br, $J = 6.3$ Hz, 1 H), 5.12 (d, $J = 17$ Hz, 1 H), 5.32 (d, $J = 10$ Hz, 1 H), 5.72 (td, $J = 10$, 17 Hz, 1 H). ^{13}C-NMR δ 24.3 (t), 25.0 (q), 25.8 (t), 25.9 (q), 34.4 (t), 43.2 (d), 43.6 (t), 45.6 (t), 46.7 (t), 48.6 (d), 66.7 (t), 75.3 (d), 108.3 (s), 120.1 (t), 134.3 (d), 172.4 (s). Anal. Calcd: C, 60.85; H, 8.3; N, 4.43. Found: C, 60.61; H, 8.17; N, 4.29.

(2*S*,3*R*,4*S*)-3-Ethenyl-2-isopropyl-4,5-(isopropylidendioxy)pentanoic Acid Pyrrolidinamide (4d). Reaction with allylamine **1** (1 g, 4.73 mmol) following the standard procedure, reaction time: 7 d, 3-4 cycles. Chromatography: EtOAc/hexanes 1:2, $R_f = 0.11$. Yield: 0.63 g (45%). Purification *via* preparative HPLC: Eluent: 5% 2-propanol in hexanes retention time 2.51 min. $[\alpha]^{23}_D$ 26 ($c = 1$ in $CHCl_3$). IR (KBr, film) 3074, 1644 (CO), 1438, 1380, 1369, 1343 cm^{-1}. MS (EI, 70 eV, 50 °C): *m/z* 295 (M^+), 280 ($M^+ - CH_3$), 237, 194, 152, 140, 138, 98, 70. ^{1}H-NMR δ 0.84 (d, $J = 7.5$ Hz, 3 H), 0.88 (d, $J = 7.5$ Hz, 3 H), 1.2 (s, 3 H), 1.28 (s, 3 H), 1.78 (m, 4 H), 2.0 (m, br, 1 H), 2.44 (m, 2 H), 3.34 (m, 4 H), 3.54 (t, br, $J = 7$ Hz, 1 H), 3.84 (dd, $J = 6.3$, 7.5 Hz, 1 H), 4.16 (dt, br, $J = 2.5$, 6.3 Hz, 1 H), 4.92 (dd, $J = 1.1$, 17.5 Hz, 1 H), 5.0 (dd, $J = 1.1$, 10 Hz, 1 H), 5.84 (m, 1 H). ^{13}C-NMR δ 18.7 (q), 20.6 (q), 24.1 (t), 25.0 (q), 25.9 (t), 26.0 (q), 28.0 (d), 45.1 (t), 46.3 (t), 47.0 (d), 50.2 (d), 67.1 (t), 75.1 (d), 108.5 (s), 118.1 (t), 134.7 (d), 171.9 (s). Anal. Calcd: C, 69.12; H, 9.89; N, 4.74. Found: C, 69.06; H, 9.76; N, 4.5.

(2*S*,3*R*,4*S*)-2,3-Di-ethenyl-4,5-(isopropylidendioxy)pentanoic Acid Pyrrolidinamide (4e). Reaction with allylamine **1** (2 g, 9.47 mmol) following the standard procedure, reaction time: 2 d. Chromatography: EtOAc/hexanes 1:1, $R_f = 0.17$. Yield: 1.64 g (62%), mp 57 °C. Purification *via* preparative HPLC: Eluent: 9% 2-propanol in hexanes retention time 2.89 min. $[\alpha]^{23}_D$ −17.9 ($c = 1.7$ in $CHCl_3$). IR (KBr, film) 3077, 3014, 1633 (CO), 1435, 1381 cm^{-1}. MS (EI, 70 eV, 60 °C): *m/z* 279 (M^+), 264 ($M^+ - CH_3$), 221, 208, 178, 152, 139, 124, 98, 70. ^{1}H-NMR δ 1.24 (s, 3 H), 1.32 (s, 3 H), 1.8 (m, 4 H), 2.54 (dt, $J = 2.5$, 9.5 Hz, 1 H), 3.34 (m, 4 H), 3.46 (t, $J = 6.3$ Hz, 1 H), 3.54 (t, $J = 7.5$ Hz, 1 H), 3.84 (dd, $J = 6.3$, 7.5 Hz, 1 H), 4.24 (m, 1 H), 5.04 (dd, $J = 1$, 16.3 Hz, 1 H), 5.08 (dd, $J = 1$, 9.5 Hz, 1 H), 5.14 (dd, $J = 1$, 10 Hz, 1 H), 5.22 (dd, $J = 1$, 17.5 Hz, 1 H), 5.71 (td, $J = 9.5$, 17.5 Hz, 1 H), 5.79 (td, $J = 10$, 16.3 Hz, 1 H). ^{13}C-NMR δ 24.1 (t), 25.0 (q), 25.7 (t), 26.0 (q), 45.4 (t), 46.2 (t), 47.1 (d), 51.8 (d), 66.9 (t), 74.1 (d), 108.3 (s), 118.3 (t), 119.3 (t), 133.9 (d), 135.3 (d), 170.4 (s). Anal. Calcd: C, 68.79; H, 9.02; N, 5.01. Found: C, 68.44; H, 8.74; N, 4.75.

(2*S*,3*S*,4*S*)-2-Chloro-3-ethenyl-4,5-(isopropylidendioxy)pentanoic Acid Pyrrolidinamide (4h) and (2*R*,3*R*,4*S*)-2-Chloro-3-ethenyl-4,5-(isopropylidendioxy)pentanoic Acid Pyrrolidinamide (5h). Reaction with allylamine **1** (3.5 g, 16.56 mmol) following the standard procedure, reaction time: 2 d. Chromatography: EtOAc/hexanes 1:1, $R_f = 0.22$ (**4h**) and $R_f = 0.25$ (**5h**). Yield: 3.9 g (82%). Separation of the diastereomeric amides **4h** and **5h** (ratio: 60:1) *via* preparative HPLC: Eluent: 5% 2-propanol in hexanes. Major diastereomer amide **4h**: retention time 2.71 min, 3.84 g (80.7%), mp 87 °C. $[\alpha]^{23}_D$ 72.1 ($c = 1.3$ in $CHCl_3$). IR (KBr, film) 3077, 1659 (CO), 1435, 1386, 1376 cm^{-1}. MS (EI, 70 eV, 80 °C): *m/z* 287 (M^+), 272 ($M^+ - CH_3$), 252, 229, 216, 194, 186, 152, 147, 101, 98, 83, 81, 70. ^{1}H-NMR δ 1.27 (s, 3 H), 1.33 (s, 3 H), 1.82 (m, 4 H), 2.79 (dt, $J = 7$, 7.5 Hz, 1 H), 3.38 (m, 4 H), 3.58 (dd, $J = 7$, 7.5 Hz, 1 H), 3.94 (dd, $J = 7$, 7.5 Hz, 1 H), 4.42 (d, $J = 10.8$ Hz, 1 H), 4.61 (dt, $J = 2.5$, 7 Hz, 1 H), 5.16 (dd, $J = 1.3$, 18 Hz, 1 H), 5.20 (dd, $J = 1.3$, 9.5 Hz, 1 H), 5.58 (td, $J = 9.5$, 18 Hz, 1 H). ^{13}C-NMR δ 24.0 (t), 24.7 (q), 25.8 (t), 25.9 (q), 45.9 (t), 46.5 (t), 48.4 (d), 55.9 (d), 66.5 (t), 73.3 (d), 108.9 (s), 122.5 (t), 130.8 (d), 166.0 (s). Anal. Calcd: C, 58.43; H, 7.7; N, 4.87. Found: C, 58.16; H, 7.47; N, 4.66. Minor diastereomer amide **5h**: retention time 2.07 min, 0.06 g (1.3%). $[\alpha]^{23}_D$ −21.5 ($c = 1.4$ in $CHCl_3$). IR (KBr, film) 3077, 1655 (CO), 1441, 1380, 1371 cm^{-1}. MS (EI, 70 eV, 60 °C): *m/z* 287 (M^+), 272 ($M^+ - CH_3$), 252, 229, 194, 186, 152, 147, 112, 101, 98, 81, 70. HRMS (EI, 80 eV, 60 °C): calcd: 272.10535, found: 272.10525. ^{1}H-NMR δ 1.28 (s, 3 H), 1.40 (s, 3 H), 1.91 (m, 4 H), 2.68 (dt, br, $J = 5$, 9.8 Hz, 1 H), 3.47 (m, 2 H), 3.58 (m, 2 H), 3.64 (dd, $J = 6.3$, 9.4 Hz, 1 H), 3.94 (dd, $J = 6.3$, 9.4 Hz, 1 H), 4.18 (td, $J = 6.3$, 9.4 Hz, 1 H), 4.7 (d, $J = 5$ Hz, 1 H), 5.16 (dd, $J = 1.3$, 17 Hz, 1 H), 5.22 (dd, $J = 1.3$, 10 Hz, 1 H), 6.16 (td, $J = 10$, 17 Hz, 1 H). ^{13}C-NMR δ 24.2 (t), 25.4 (q), 26.1 (t), 26.8 (q), 46.1 (t), 46.6 (t), 53.4 (d), 54.6 (d), 68.1 (t), 75.4 (d), 109.4 (s), 120.3 (t), 133.0 (d), 166.1 (s).

(2*S*,3*S*,4*S*)-2-(Benzyloxy)-3-ethenyl-4,5-(isopropylidendioxy)pentanoic Acid Pyrrolidinamide (4i) and (2*R*/*S*,3*R*,4*S*)-2-(Benzyloxy)-3-ethenyl-4,5-(isopropylidendioxy)-pentanoic Acid Pyrrolidinamide (5/7i). Reaction with allylamine **1** (2.5 g, 11.83 mmol) following the standard procedure, reaction time: 2 d. Chromatography: EtOAc/hexanes 1:1, $R_f = 0.17$ (**4i**) and $R_f = 0.21$ (**5/7i**). Yield: 3.53 g (83%). Separation of the diastereomeric amides **4i** and **5/7i** (ratio: 20:2:1) *via* preparative HPLC: Eluent: 5% 2-propanol in hexanes. Major diastereomer amide **4i**: retention time 4.52 min, 3.07 g (72.2%). $[\alpha]^{23}_D$ −20.6 ($c = 1.3$ in $CHCl_3$). IR (KBr, film) 3064, 3030, 1650 (CO), 1440, 1380, 1369 cm^{-1}. MS (EI, 70 eV, 100 °C): *m/z* 359 (M^+), 344 ($M^+ - CH_3$), 268, 152, 128, 101, 98, 91. ^{1}H-NMR δ 1.38 (s, 3 H), 1.40 (s, 3 H), 1.80 (m, 4 H), 2.7 (dt, $J = 3.8$, 10 Hz, 1 H), 3.18 (m, 1 H), 3.42 (m, 3 H), 3.66 (t, br, $J = 7.5$ Hz, 1 H), 4.02 (t, br, $J = 6.3$ Hz, 1 H), 4.2 (d, $J = 10$ Hz, 1 H), 4.48 (d, $J = 11.3$ Hz, 1 H), 4.56 (dt, $J = 3.8$, 7 Hz, 1 H), 4.68 (d, $J = 11.3$ Hz, 1 H), 5.12 (d, br, $J = 16.3$ Hz, 1 H), 5.16 (d, br, $J = 10$ Hz, 1 H), 5.76 (td, $J = 10$, 16.3 Hz, 1 H), 7.36 (m, 5 H). ^{13}C-NMR δ 23.5 (t), 25.1 (q), 25.9 (t), 26.0 (q), 45.6 (t), 45.8 (t), 49.2 (d), 67.0 (t), 71.6 (t), 73.7 (d), 77.9 (d), 108.3 (s), 120.2 (t), 127.6 (d), 127.7 (d), 128.1 (d), 131.5 (d), 137.4 (s), 169.0 (s). Anal. Calcd: C, 70.17; H, 8.13; N, 3.9. Found: C, 69.98; H, 7.9; N, 3.89. Minor diastereomer amides **5/7i** (ratio 2:1, not separable): retention time 3.48 min, 0.46 g (10.8%). Data of the major compound: IR (KBr, film) 3066, 3030, 1650 (CO), 1497, 1453 1439 cm^{-1}. MS (EI, 70 eV, 80 °C): *m/z* 359 (M^+), 344 ($M^+ - CH_3$), 268, 259, 253, 152, 128, 101, 98, 91, 70. HRMS (EI, 80 eV, 90 °C): calcd: 344.18618, found: 344.18626. ^{1}H-NMR δ 1.32 (s, 3 H), 1.40 (s, 3 H), 1.86 (m, 4 H), 2.84 (m, 1 H), 3.18 (m, 4 H), 3.48 (m, 1 H), 3.8 (t, $J = 7.5$ Hz, 1 H), 3.96 (dd, $J = 6.3$, 7.5 Hz, 1 H), 4.24 (d, $J = 5$ Hz, 1 H), 4.32 (q, br, $J = 6.3$ Hz, 1 H), 4.4 (d, $J = 11.3$ Hz, 1 H), 4.68 (d, $J = 11.3$ Hz, 1 H), 5.18 (d, br, $J = 17.5$ Hz, 1 H), 5.22 (d, br, $J = 10$ Hz, 1 H), 5.88 (td, $J = 10$, 17.5 Hz, 1 H), 7.34 (m, 5 H). ^{13}C-NMR δ 23.4 (t), 25.2 (q), 26.2 (t), 26.4 (q), 45.9 (t), 46.1 (t), 49.2 (d), 66.9 (t), 71.6 (t),

74.8 (d), 78.6 (d), 108.4 (s), 118.7 (t), 127.6 (d), 127.7 (d), 128.1 (d), 133.5 (d), 137.3 (s), 168.5 (s).

(1′*S*,1′*R*,2*R*)-2-[1-(3,3-Dimethyl-2,4-dioxolanyl)-2-propenyl]-3,5-hexadienoic Acid Pyrrolidinamide (6f). Reaction with allylamine **1** (1.5 g, 7.1 mmol) following the standard procedure, reaction time: 2 d. Chromatography: EtOAc/hexanes 1:2, $R_f = 0.18$. Yield: 1.3 g (60%). Purification *via* preparative HPLC, the product should not be stored for more than one week because of its low stability! Eluent: 5% 2-propanol in hexanes retention time 2.29 min. $[\alpha]^{23}_D$ −34.7 ($c = 1$ in $CHCl_3$). IR (KBr, film) 3077, 1639 (CO), 1432, 1369 cm^{-1}. MS (EI, 70 eV, 60 °C): *m*/*z* 305 (M^+), 290 ($M^+ - CH_3$), 204, 165, 164, 152, 98, 83, 70. HRMS (EI, 80 eV, 60 °C): calcd: 305.19907, found: 305.19913. ^{1}H-NMR δ 1.3 (s, 3 H), 1.4 (s, 3 H), 1.83 (m, 2 H), 1.92 (m, 2 H), 2.65 (dt, $J = 2$, 10 Hz, 1 H), 3.42 (m, 3 H), 3.49 (m, 2 H), 3.6 (t, $J = 7.5$ Hz, 1 H), 3.92 (dd, $J = 6.3$, 7.5 Hz, 1 H), 4.24 (dt, br, $J = 2.5$, 7 Hz, 1 H), 5.07 (dd, $J = 2$, 10.5 Hz, 1 H), 5.15 (dd, $J = 2$, 16.3 Hz, 1 H), 5.16 (dd, $J = 2$, 11 Hz, 1 H), 5.19 (dd, $J = 2$, 15 Hz, 1 H), 5.74 (m, 2 H), 6.25 (dd, $J = 11$, 15 Hz, 1 H), 6.34 (td, $J = 10.5$, 16.3 Hz, 1 H). ^{13}C-NMR δ 24.0 (t), 24.9 (q), 25.6 (t), 25.9 (q), 45.4 (t), 46.2 (t), 47.5 (d), 50.5 (d), 66.7 (t), 74.2 (d), 108.2 (s), 116.6 (t), 119.3 (t), 130.6 (d), 133.7 (d), 134.1 (d), 136.3 (d), 170.3 (s).

(2*S*,3*R*,4*S*)-3-Ethenyl-4,5-(isopropylidendioxy)-2-phenylpentanoic Acid Pyrrolidinamide (6g). Reaction with allylamine **1** (1 g, 4.73 mmol) following the standard procedure, reaction time: 7 d, 3-4 cycles. Chromatography: EtOAc/hexanes 1:2, $R_f = 0.2$. Yield: 0.81 g (52%), mp 113 °C. Purification *via* preparative HPLC: Eluent: 2% 2-propanol in hexanes retention time 3.99 min. $[\alpha]^{23}_D$ −23.3 ($c = 1.4$ in $CHCl_3$). IR (KBr, film) 3075, 3040, 1632 (CO), 1602, 1491, 1456 cm^{-1}. MS (EI, 70 eV, 90 °C): *m*/*z* 329 (M^+), 314 ($M^+ - CH_3$), 271, 258, 242, 228, 189, 160, 129, 118, 98, 91, 70. ^{1}H-NMR δ 1.18 (s, 3 H), 1.38 (s, 3 H), 1.78 (m, 3 H), 1.92 (m, 1 H), 2.98 (t, br, $J = 10.5$ Hz, 1 H), 3.4 (m, 4 H), 3.6 (m, 3 H), 3.9 (d, $J = 10.5$ Hz, 1 H), 5.22 (d, br, $J = 10$ Hz, 1 H), 5.28 (d, br, $J = 17$ Hz, 1 H), 5.84 (td, $J = 10$, 17 Hz, 1 H), 7.32 (m, 3 H), 7.54 (m, 2 H). ^{13}C-NMR δ 24.0 (t), 24.9 (q), 25.8 (t), 26.1 (q), 45.6 (t), 46.2 (t), 48.4 (d), 52.4 (d), 66.7 (t), 74.1 (d), 108.2 (s), 119.6 (t), 127.1 (d), 128.3 (d), 129.0 (d), 134.5 (d), 136.9 (s), 170.2 (s). Anal. Calcd: C, 72.92; H, 8.26; N, 4.25. Found: C, 72.9; H, 8.22; N, 4.2.

(4*S*,5*S*)-4-Ethenyl-5-(hydroxymethyl)-2(3*H*)-furanone (8a). The 2-chloro amide **4h** (0.33 g, 1.15 mmol) was dissolved in HOAc (8 mL). Then, the mixture was heated to 105 °C, with stirring, and Zn (powder, 0.4 g, 6.12 mmol) was added. After about 1 h, the reaction was found to be complete. After cooling to rt, H_2O (30 mL, 0 °C) was added. The mixture was neutralized with solid $NaHCO_3$ and then extracted with CH_2Cl_2 (5 × 15 mL). The organic layers were dried ($MgSO_4$), and the solvent was removed. The crude material was purified by chromatography on silica gel (EtOAc/hexanes 1:1) to give lactone **8a** (134 mg, 82%) and the corresponding 5-acetoxymethyl lactone (impure, 18 mg, 8.5%). For spectral data see ref 21.

Standard Procedure for the Lactonization and, If Need Be, the Silylation. The amide (1 mmol) was dissolved in methanol (7 mL) and heated to 60 °C. TFA (2.5 mL) was added. The mixture was stirred at 60 °C to 70 °C (about 16 h), until the reaction was found to be complete. Then, the solvent was removed and the crude material was vacuum-dried. The hydroxy lactone was either purified via column chromatography on silica gel or directly used for the protection step.

Silylation. The hydroxy lactone was dissolved in dry CH_2Cl_2 (10 mL) and subsequently treated with imidazole (272 mg, 4 mmol) and TBDMSCl (301 mg, 2 mmol). After stirring for 12 h at rt the reaction was complete. The mixture was quenched with H_2O (25 mL), and then the aqueous layer was extracted with CH_2Cl_2 (5 × 10 mL). The combined organic layers were dried ($MgSO_4$), and after concentration the residue was purified *via* chromatography on silica gel.

(3*S*,4*R*,5*S*)-5-[(*tert*-Butyldimethylsilyloxy)methyl]-3-(2-chloroethyl)-4-ethenyl-2(3*H*)-furanone (8c). Reaction with amide **4c** (0.3 g, 0.95 mmol) following the standard procedure. Chromatography: EtOAc/hexanes 1:20, $R_f = 0.22$. Yield: 279 mg (92%). $[\alpha]^{23}_D$ 68 ($c = 2.1$ in $CHCl_3$). IR (KBr, film) 3082, 1780 (CO), 1472, 1361 cm^{-1}. MS (EI, 70 eV, 100 °C): *m*/*z* 318 (M^+), 303 ($M^+ - CH_3$), 263, 261, 243, 233, 197, 155, 117, 105, 93, 89, 81, 75. ^{1}H-NMR δ 0.02 (s, 3 H), 0.04 (s, 3 H), 0.86 (s, 9 H),1.82 (tdd, $J = 6$, 8, 13.8 Hz, 1 H), 2.17 (tdd, $J = 6$, 8, 13.8 Hz, 1 H), 3.01 (td, $J = 5$, 7.5 Hz, 1 H), 3.16 (ddd, $J = 6$, 8, 11.3 Hz, 1 H), 3.56 (ddd, $J = 6$, 8, 11.3 Hz, 1 H), 3.62 (dd, $J = 5$, 11.3 Hz, 1 H), 3.73 (m, 1 H), 3.74 (dd, $J = 5.5$, 11.3 Hz, 1 H), 4.45 (q, $J = 5$ Hz, 1 H), 5.22 (dd, $J = 0.5$, 16.8 Hz, 1 H), 5.26 (dd, $J = 0.5$, 10 Hz, 1 H), 5.52 (td, $J = 10$, 16.8 Hz, 1 H). ^{13}C-NMR δ −5.6 (q), 18.1 (s), 25.6 (q), 28.6 (t), 41.5 (d), 42.2 (t), 46.2 (d), 62.0 (t), 81.2 (d), 120.9 (t), 129.9 (d), 177.0 (s). Anal. Calcd: C, 56.49; H, 8.53. Found: C, 56.35; H, 8.44.

(3*S*,4*R*,5*S*)-5-[(*tert*-Butyldimethylsilyloxy)methyl]-4-ethenyl-3-isopropyl-2(3*H*)-furanone (8d). Reaction with amide **4d** (0.1 g, 0.34 mmol) following the standard procedure. Chromatography: EtOAc/hexanes 1:15, $R_f = 0.23$. Yield: 92 mg (91%). Purification *via* preparative HPLC: Eluent: 5% 2-propanol in hexanes retention time 3.0 min. $[\alpha]^{23}_D$ 28.7 ($c = 0.7$ in $CHCl_3$). IR (KBr, film) 3081, 1781 (CO), 1472, 1388 cm^{-1}. MS (EI, 70 eV, 60 °C): *m*/*z* 298 (M^+), 283 ($M^+ - CH_3$), 263, 241, 211, 189, 155, 147, 117, 105, 95, 89, 75. ^{1}H-NMR δ 0.04 (2 × s, 6 H), 0.86 (s, 9 H), 0.9 (d, $J = 6.5$ Hz, 3 H), 1.22 (d, $J = 6.5$ Hz, 3 H), 1.82 (m, 1 H), 2.3 (dd, $J = 6.3$, 7.5 Hz, 1 H), 3.1 (ddd, $J = 5.5$, 6.3, 10 Hz, 1 H), 3.6 (dd, $J = 5.5$, 11.3 Hz, 1 H), 3.72 (dd, $J = 6.3$, 11.3 Hz, 1 H), 4.32 (q, br, $J = 6$ Hz, 1 H), 5.2 (dd, $J = 1.3$, 16.3 Hz, 1 H), 5.24 (dd, $J = 1.3$, 10 Hz, 1 H), 5.56 (td, $J = 10$, 16.3 Hz, 1 H). ^{13}C-NMR δ −5.8 (q), −5.5 (q), 18.1 (s), 20.6 (q), 20.9 (q), 25.7 (q), 25.8 (d), 47.1 (d), 51.9 (d), 62.3 (t), 80.6 (d), 120.4 (t), 130.5 (d), 176.5 (s). Anal. Calcd: C, 64.38; H, 10.13. Found: C, 64.3; H, 10.07.

(3*S*,4*R*,5*S*)-3,4-Di-ethenyl-5-(hydroxymethyl)-2(3*H*)-furanone (8e). Reaction with amide **4e** (0.42 g, 1.5 mmol) following the standard procedure without the silylation step. Chromatography: EtOAc/hexanes 1:2, $R_f = 0.2$. Yield: 212 mg (84%). Purification *via* preparative HPLC: Eluent: 7% 2-propanol in hexane retention time 3.91 min, about 30 mg of the impure α,β-unsaturated lactone could be separated (retention time 3.37 min). The product is unstable and decomposes in less than two days. $[\alpha]^{23}_D$ 28.3 ($c = 2$ in $CHCl_3$). IR (KBr, film) 3438 (br, OH), 3084, 3019, 1768 (CO), 1643, 1426 cm^{-1}. MS (EI, 70 eV, 60 °C): *m*/*z* 168 (M^+), 167, 137, 124, 108, 93, 91, 79, 68. ^{1}H-NMR δ 3.3 (ddd, $J = 5$, 7.5, 10 Hz, 1 H), 3.54 (t, $J = 7.5$ Hz, 1 H), 3.7 (dd, $J = 4$, 12.5 Hz, 1 H), 3.8 (dd, $J = 7.5$, 12.5 Hz, 1 H), 4.16 (s, br, 1 H, OH), 4.64 (ddd, $J = 4$, 5, 7.5 Hz, 1 H), 5.2 (dd, $J = 1.2$, 16.3 Hz, 1 H), 5.26 (dd, $J = 1.2$, 10 Hz, 1 H), 5.32 (dd, $J = 1$, 17 Hz, 1 H), 5.36 (dd, $J = 1$, 10.5 Hz, 1 H), 5.64 (td, $J = 10$, 16.3 Hz, 1 H), 5.72 (ddd, $J = 7.5$, 10.5, 17 Hz, 1 H). ^{13}C-NMR δ 47.6 (d), 49.0 (d), 62.1 (t), 81.9 (d), 120.4 (t), 121.2 (t), 129.5 (d), 130.5 (d), 176.3 (s). Anal. Calcd: C, 64.27; H, 7.19. Found: C, 63.95; H, 6.88.

(3*S*,4*S*,5*S*)-3-Chloro-4-ethenyl-5-(hydroxymethyl)-2(3*H*)-furanone and (3*S*,4*S*,5*S*)-5-[(*tert*-Butyldimethylsilyloxy)-methyl]-3-chloro-4-ethenyl-2(3*H*)-furanone (8h). Hydroxy lactone **8h**[a]: Reaction with amide **4h** (0.5 g, 1.74 mmol) following the standard procedure without the silylation step. Chromatography: EtOAc/hexanes 1:1, $R_f = 0.14$. Yield: 291 mg (95%). $[\alpha]^{23}_D$ 33.6 ($c = 2.4$ in $CHCl_3$). IR (KBr, film) 3404 (br, OH), 3086, 1786 (CO), 1642, 1427 cm^{-1}. MS (EI, 70 eV, 60 °C): *m*/*z* 176 (M^+), 145, 141, 102, 88, 81, 67, 53. ^{1}H-NMR δ 3.14 (s, br, 1 H, OH), 3.52 (ddd, $J = 6.2$, 7.5, 10 Hz, 1 H), 3.74 (dd, $J = 3$, 12.5 Hz, 1 H), 3.85 (dd, $J = 8.3$, 12.5 Hz, 1 H), 4.7 (ddd, $J = 3$, 6.3, 8.3 Hz, 1 H), 4.78 (d, $J = 7.5$ Hz, 1 H), 5.34 (dd, $J = 1$, 16.3 Hz, 1 H), 5.38 (dd, $J = 1$, 10 Hz, 1 H), 5.68 (td, $J = 10$, 16.3 Hz, 1 H). ^{13}C-NMR δ 47.8 (d), 55.0 (d), 62.1 (t), 81.8 (d), 122.2 (t), 128.6 (d), 171.9 (s). Anal. Calcd: C, 47.61; H, 5.14. Found: C, 47.49; H, 5.01. Silyloxy lactone **8h**[b]: Reaction with amide **4h** (0.3 g, 1.04 mmol) following the standard procedure, imidazole was replaced by pyridine. Chromatography: EtOAc/hexanes 1:20, $R_f = 0.17$. Yield: 267 mg (88%). $[\alpha]^{23}_D$ 29.8 ($c = 1.7$ in $CHCl_3$). IR (KBr, film) 3086, 1796 (CO), 1643, 1472 cm^{-1}. MS (EI, 70 eV, 50 °C): *m*/*z* 290 (M^+), 275 ($M^+ - CH_3$), 233, 203, 189, 123, 117, 101, 93, 75. ^{1}H-NMR δ 0.01 (2 × s, 6 H), 0.84 (s, 9 H), 3.44 (ddd, $J = 5.5$, 7.5, 10 Hz, 1 H), 3.68 (dd, $J = 5$, 11.3 Hz, 1 H), 3.78 (dd, $J =$

6, 11.3 Hz, 1 H), 4.54 (q, br, J = 5.5 Hz, 1 H), 4.66 (d, J = 7.5 Hz, 1 H), 5.26 (d, br, J = 16.3 Hz, 1 H), 5.32 (d, br, J = 10 Hz, 1 H), 5.64 (td, J = 10, 16.3 Hz, 1 H). ^{13}C-NMR δ −5.6 (q), −5.5 (q), 18.1 (s), 25.7 (q), 48.0 (d), 55.0 (d), 62.2 (t), 81.1 (d), 121.9 (t), 128.9 (d), 171.3 (s). Anal. Calcd: C, 53.68; H, 7.97. Found: C, 53.59; H, 7.9.

(3*S*,4*S*,5*S*)-3-(Benzyloxy)-4-ethenyl-5-(hydroxymethyl)-2(3*H*)-furanone (8i). Reaction with amide **4i** (0.5 g, 1.39 mmol) following the standard procedure without the silylation step. Chromatography: EtOAc/hexanes 1:1, R_f = 0.17. Yield: 318 mg (92%). $[\alpha]^{23}_D$ −4 (c = 1.2 in $CHCl_3$). IR (KBr, film) 3442 (br, OH), 3087, 3065, 3032, 1788 (CO), 1642, 1497 cm^{-1}. MS (EI, 70 eV, 100 °C): m/z 248 (M^+), 238, 189, 160, 142, 102, 99, 91, 65. ^{1}H-NMR δ 3.32 (td, br, J = 6.3, 10 Hz, 1 H), 3.64 (dd, J = 4.5, 12.5 Hz, 1 H), 3.7 (s, br, 1 H, OH), 3.76 (dd, J = 7.5, 12.5 Hz, 1 H), 4.28 (d, J = 6.3 Hz, 1 H), 4.48 (m, 1 H), 4.72 (AB-system, J = 11.3 Hz, 2 H), 5.28 (d, br, J = 16.3 Hz, 1 H), 5.32 (d, br, J = 10 Hz, 1 H), 5.74 (td, J = 10, 16.3 Hz, 1 H), 7.32 (m, 5 H). ^{13}C-NMR δ 46.6 (d), 62.3 (t), 72.0 (t), 75.0 (d), 80.1 (d), 121.1 (t), 127.9 (d), 128.0 (d), 128.3 (d), 128.6 (d), 136.4 (s), 173.8 (s). Anal. Calcd: C, 67.73; H, 6.5. Found: C, 67.58; H, 6.37.

(3*R*,4*R*,5*S*) 3-(Benzyloxy)-5-[(*tert*-butyldimethylsilyloxy)methyl]-4-ethenyl-2(3*H*)-furanone (9i) and (3*S*,4*R*,5*S*)-3-(Benzyloxy)-5-[(*tert*-butyldimethylsilyloxy)methyl]-4-ethenyl-2(3*H*)-furanone (11i). Reaction with amide **5/7i** (0.2 g, 0.56 mmol) following the standard procedure. Chromatography: EtOAc/hexanes 1:1, R_f = 0.22 (**9i**) and R_f = 0.11 (**11i**). Yield: 162 mg (82%). Separation of the diastereomeric lactones **9i** and **11i** (ratio: 3:1) *via* preparative column chromatography. Major diastereomer lactone **9i**: 121 mg (61.5%). $[\alpha]^{23}_D$ 110.7 (c = 1.7 in $CHCl_3$). IR (KBr, film) 3084, 3066, 3032, 1784 (CO), 1643, 1497 cm^{-1}. MS (EI, 70 eV, 80 °C): m/z 362 (M^+), 345, 319, 305, 301, 277, 256, 199, 171, 117, 91, 73. ^{1}H-NMR δ 0.04 (2 × s, 6 H), 0.84 (s, 9 H), 3.16 (m, 1 H), 3.68 (dd, J = 2.5, 11.5 Hz, 1 H), 3.9 (dd, J = 2.5, 11.5 Hz, 1 H), 4.24 (d, J = 6.5 Hz, 1 H), 4.4 (m, 1 H), 4.7 (d, J = 11.3 Hz, 1 H), 4.84 (d, J = 11.3 Hz, 1 H), 5.22 (d, br, J = 16.5 Hz, 1 H), 5.26 (d, br, J = 10 Hz, 1 H), 5.98 (ddd, J = 8.8, 10, 16.5 Hz, 1 H), 7.36 (m, 5 H). ^{13}C-NMR δ −5.8 (q), −5.7 (q), 18.0 (s), 25.6 (q), 45.7 (d), 62.3 (t), 71.9 (t), 75.1 (d), 83.0 (d), 119.1 (t), 127.8 (d), 128.3 (d), 131.9 (d), 136.9 (s), 173.9 (s). Anal. Calcd: C, 66.26; H, 8.34. Found: C, 66.02; H, 8.11. Minor diastereomer lactone **11i**: yield 41 mg (20.5%). $[\alpha]^{23}_D$ 4 (c = 1.4 in $CHCl_3$). IR (KBr, film) 3087, 3065, 3032, 1790 (CO), 1645, 1497 cm^{-1}. MS (EI, 70 eV, 60 °C): m/z 362 (M^+), 345, 337, 277, 256, 233, 199, 185, 171, 147, 117, 91, 75, 73. ^{1}H-NMR δ 0.08 (s, 6 H), 0.88 (s, 9 H), 3.2 (q, br, J = 10 Hz, 1 H), 3.68 (dd, J = 3.8, 11.3 Hz, 1 H), 3.9 (dd, J = 2.5, 11.3 Hz, 1 H), 4.06 (m, 1 H), 4.12 (d, J = 10 Hz, 1 H), 4.8 (d, J = 12.3 Hz, 1 H), 5.0 (d, J = 12.3 Hz, 1 H), 5.24 (d, br, J = 10.5 Hz, 1 H), 5.28 (d, br, J = 17.5 Hz, 1 H), 5.68 (ddd, J = 8.8, 10.5, 17.5 Hz, 1 H), 7.36 (m, 5 H). ^{13}C-NMR δ −5.5 (q), −5.4 (q), 18.3 (s), 25.8 (q), 47.3 (d), 61.6 (t), 72.1 (d), 77.5 (t), 80.0 (d), 120.1 (t), 128.0 (d), 128.1 (d), 128.4 (d), 133.5 (d), 137.0 (s), 173.9 (s). Anal. Calcd: C, 66.26; H, 8.34. Found: C, 66.0; H, 8.03.

(3*R*,4*R*,5*S*)-5-[(*tert*-Butyldimethylsilyloxy)methyl]-3-(2-chloroethyl)-4-ethenyl-2(3*H*)-furanone (10c). Reaction with amide **6c** (0.16 g, 0.51 mmol) following the standard procedure. Chromatography: EtOAc/hexanes 1:20, R_f = 0.1. Yield: 145 mg (90%). $[\alpha]^{23}_D$ 52 (c = 2.8 in $CHCl_3$). IR (KBr, film) 3083, 1773 (CO), 1471, 1346 cm^{-1}. MS (EI, 70 eV, 100 °C): m/z 318 (M^+), 303 ($M^+ - CH_3$), 263, 261, 233, 231, 157, 123, 155, 117, 107, 93, 89, 81, 75. ^{1}H-NMR δ 0.04 (s, 3 H), 0.05 (s, 3 H), 0.87 (s, 9 H),1.84 (m, 1 H), 2.13 (m, 1 H), 2.93 (td, J = 8, 10 Hz, 1 H), 3.03 (td, J = 6.3, 11.3 Hz, 1 H), 3.68 (td, J = 6.3, 11.3 Hz, 1 H), 3.74 (d, J = 11.3 Hz, 1 H), 3.8 (td, J = 6.3, 11.3 Hz, 1 H), 3.84 (dd, J = 2.5, 11.3 Hz, 1 H), 4.38 (d, br, J = 8 Hz, 1 H), 5.22 (d, br, J = 10 Hz, 1 H), 5.26 (d, br, J = 17.5 Hz, 1 H), 5.96 (td, J = 10, 17.5 Hz, 1 H). ^{13}C-NMR δ −5.9 (q), 17.9 (s), 25.6 (q), 33.2 (t), 41.3 (d), 42.0 (t), 49.7 (d), 62.3 (t), 80.0 (d), 120.0 (t), 134.4 (d), 178.0 (s). Anal. Calcd: C, 56.49; H, 8.53. Found: C, 56.41; H, 8.4.

(E)-(3*R*,4*R*,5*S*)-3-Butadienyl-4-ethenyl-5-(hydroxymethyl)-2(3*H*)-furanone (10f). Reaction with amide **6f** (0.46 g, 1.51 mmol) following the standard procedure without the silylation step. Chromatography: EtOAc/hexanes 1:2, R_f = 0.18. Yield: 249 mg (85%). The product is unstable and decomposes in less than one day. $[\alpha]^{23}_D$ 33 (c = 0.8 in $CHCl_3$). IR (KBr, film) 3439 (br, OH), 3083, 3016, 1770 (CO), 1642, 1425 cm^{-1}. MS (EI, 70 eV, 80 °C): m/z 194 (M^+), 165, 150, 134, 119, 105, 95, 91, 85, 83, 79. HRMS (EI, 80 eV, 80 °C): calcd: 194.09430, found: 194.09415. ^{1}H-NMR δ 3.18 (ddd, J = 8.4, 9.5, 11.3 Hz, 1 H), 3.5 (s, br, 1 H, OH), 3.53 (dd, J = 7.4, 11.3 Hz, 1 H), 3.76 (dd, J = 2.7, 12.7 Hz, 1 H), 3.91 (dd, J = 2.7, 12.7 Hz, 1 H), 4.53 (td, J = 2.7, 8.4 Hz, 1 H), 5.09 (dd, J = 1.5, 9.5 Hz, 1 H), 5.22 (m, 3 H), 5.59 (dd, J = 7.4, 14.6 Hz, 1 H), 5.94 (td, J = 9.5, 18.1 Hz, 1 H), 6.21 (dd, J = 10.4, 14.6 Hz, 1 H), 6.32 (td, J = 10.3, 16.5 Hz, 1 H). ^{13}C-NMR δ 47.7 (d), 49.1 (d), 61.5 (t), 81.0 (d), 117.6 (t), 119.8 (t), 127.3 (d), 133.4 (d), 135.0 (d), 136.0 (d), 177.3 (s).

(3*S*,4*R*,5*S*)-5-[(*tert*-Butyldimethylsilyloxy)methyl]-4-ethenyl-3-phenyl-2(3*H*)-furanone (10g). Reaction with amide **6g** (0.26 g, 0.79 mmol) following the standard procedure. Chromatography: EtOAc/hexanes 1:20, R_f = 0.12. Yield: 241 mg (92%). $[\alpha]^{23}_D$ 58.5 (c = 0.8 in $CHCl_3$). IR (KBr, film) 3084, 3065, 3031, 1776 (CO), 1492, 1471 cm^{-1}. MS (EI, 70 eV, 60 °C): m/z 332 (M^+), 275, 117, 89, 73. ^{1}H-NMR δ 0.12 (2 × s, 6 H), 0.96 (s, 9 H), 3.36 (td, J = 8.5, 11.3 Hz, 1 H), 3.86 (dd, J = 1.2, 11.3 Hz, 1 H), 3.96 (dd, J = 2.5, 11.3 Hz, 1 H), 4.04 (d, J = 11.3 Hz, 1 H), 4.54 (d, br, J = 8.3 Hz, 1 H), 5.08 (d, br, J = 17 Hz, 1 H), 5.18 (dd, J = 1.2, 10 Hz, 1 H), 6.0 (ddd, J = 8.8, 10, 17 Hz, 1 H), 7.28 (m, 5 H). ^{13}C-NMR δ −5.9 (q), −5.8 (q), 18.0 (s), 25.7 (q), 51.8 (d), 52.2 (d), 62.6 (t), 79.9 (d), 120.2 (t), 127.3 (d), 128.4 (d), 128.6 (d), 133.5 (d), 136.4 (s), 176.7 (s). Anal. Calcd: C, 68.63; H, 8.49. Found: C, 68.6; H, 8.44.

Standard Procedure for the Iodocyclization. The amide (1.5 mmol) or the hydroxy lactone (1.5 mmol) was dissolved in DME (6 mL) and H_2O (6 mL). With exclusion of light, I_2 (0.76 g, 3 mmol) was added. The mixture was vigorously stirred at rt, until the reaction was found to be complete. Then, the excess of I_2 was reduced with saturated aqueous $Na_2S_2O_3$ (5 mL), and H_2O (20 mL) was added. The mixture was extracted with Et_2O (4 × 15 mL), the organic layers were dried ($MgSO_4$), and the solvent was removed. The crude material was purified *via* column chromatography on silica gel, and the diastereomers were separated *via* preparative HPLC.

(1′*R*,3*S*,4*R*,5*R*)-3-Chloro-4-(3,3-dimethyl-2,4-dioxolanyl)-5-(iodomethyl)-2(3*H*)-furanone (14) and (1′*R*,3*S*,4*R*,5*S*)-3-Chloro-4-(3,3-dimethyl-2,4-dioxolanyl)-5-(iodomethyl)-2(3*H*)-furanone (15). Reaction with amide **4h** (0.63 g, 2.19 mmol) following the standard procedure, reaction time: 12 h. Chromatography: EtOAc/hexanes 1:5, R_f = 0.22 (**12**) and R_f = 0.15 (**13**). Yield: 639 mg (81%). Separation of the diastereomeric amides **14** and **15** (ratio: 54:46) *via* preparative HPLC: Eluent: 5% 2-propanol in hexanes. Amide **15**: retention time 1.06 min, 294 mg (37.2%), mp 110 °C. $[\alpha]^{23}_D$ −81.4 (c = 0.9 in $CHCl_3$). IR (KBr, film) 1793 (CO), 1454, 1430, 1381 cm^{-1}. MS (EI, 70 eV, 80 °C): m/z 360 (M^+), 345 ($M^+ - CH_3$), 303, 285, 233, 175, 101, 72. ^{1}H-NMR δ 1.36 (s, 3 H), 1.40 (s, 3 H), 2.92 (q, br, J = 9.5 Hz, 1 H), 3.5 (dd, J = 5.5, 11.3 Hz, 1 H), 3.64 (dd, J = 3.8, 11.3 Hz, 1 H), 3.92 (dd, J = 5.5, 8.3 Hz, 1 H), 4.16 (dd, J = 5.5, 8.3 Hz, 1 H), 4.42 (td, J = 5.5, 10 Hz, 1 H), 4.66 (d, J = 10 Hz, 1 H), 4.86 (ddd, J = 3.8, 5.5, 10 Hz, 1 H). ^{13}C-NMR δ 3.1 (t), 25.5 (q), 26.6 (q), 51.2 (d), 51.5 (d), 67.7 (t), 73.1 (d), 77.8 (d), 109.6 (s), 170.4 (s). Anal. Calcd: C, 33.31; H, 3.91. Found: C, 33.09; H, 3.71. Amide **14**: retention time 1.91 min, 345 mg (43.8%), mp 84 °C. $[\alpha]^{23}_D$ 22 (c = 1.5 in $CHCl_3$). IR (KBr, film) 1792 (CO), 1482, 1455, 1382 cm^{-1}. MS (EI, 70 eV, 100 °C): m/z 360 (M^+), 345 ($M^+ - CH_3$), 303, 285, 169, 147, 101, 72. ^{1}H-NMR δ 1.38 (s, 3 H), 1.47 (s, 3 H), 2.7 (q, br, J = 7.5 Hz, 1 H), 3.54 (dd, J = 4.5, 11.3 Hz, 1 H), 3.73 (dd, J = 4.5, 11.3 Hz, 1 H), 3.96 (dd, J = 5, 8.8 Hz, 1 H), 4.2 (dd, J = 6.3, 8.8 Hz, 1 H), 4.26 (q, br, J = 6.3 Hz, 1 H), 4.32 (m, 1 H), 4.42 (d, J = 8.5 Hz, 1 H). ^{13}C-NMR δ 7.5 (t), 24.9 (q), 26.3 (q), 53.2 (d), 53.6 (d), 67.1 (t), 75.3 (d), 78.4 (d), 110.0 (s), 169.9 (s). Anal. Calcd: C, 33.31; H, 3.91. Found: C, 33.02; H, 3.62.

(3a*R*,4*R*,6a*S*)-4-(Iodomethyl)furo[3,4-*b*]furan-2-one (18a). Reaction with lactone **8a** (0.2 g, 1.41 mmol) following the standard procedure, reaction time: 2 h. Chromatogra-

phy: EtOAc/hexanes 1:2, R_f = 0.21. Yield: 310 mg (82%). Separation of the lactone **18a** from a mixture of **18a** and **19a** (ratio: 5:1) *via* preparative HPLC: Eluent: 12% 2-propanol in hexanes. Lactone **18a**: retention time 2.6 min, 207 mg (54.8%), mp 107 °C. $[\alpha]^{23}_D$ 16.2 (c = 2 in $CHCl_3$). IR (KBr, film) 1752 (CO), 1424, 1351 cm^{-1}. MS (EI, 70 eV, 90 °C): m/z 268 (M^+), 181, 141, 127, 99, 83. ^{1}H-NMR δ 2.56 (m, 1 H), 2.91 (m, 1 H), 2.93 (m, 1 H), 3.25 (dd, J = 7.5, 10 Hz, 1 H), 3.3 (dd, J = 5, 10 Hz, 1 H), 3.91 (td, J = 5, 7.5 Hz, 1 H), 4.09 (dd, J = 2, 11.3 Hz, 1 H), 4.21 (dd, J = 4.5, 11.3 Hz, 1 H), 5.13 (ddd, J = 2, 4.5, 6 Hz, 1 H). ^{13}C-NMR δ 6.7 (t), 33.6 (t), 44.7 (d), 72.5 (t), 84.1 (d), 84.5 (d), 175.3 (s). Anal. Calcd: C, 31.37; H, 3.38. Found: C, 31.15; H, 3.11. The complete separation of the minor diastereomer **19a** (retention time 2.7 min) from the major compound failed, 103 mg of a 1:1 mixture of **18a** and **19a** remained.

(3*S*,3a*R*,4*R*,6a*S*)-4-(Iodomethyl)-3-methylfuro[3,4-*b*]furan-2-one (18b). Reaction with lactone **8b** (0.15 g, 0.96 mmol) following the standard procedure, reaction time: 3 h. Chromatography: EtOAc/hexanes 1:4, R_f = 0. 1. Yield: 238 mg (88%), mp 90 °C. $[\alpha]^{23}_D$ 1.7 (c = 1.2 in $CHCl_3$). IR (KBr, film) 1755 (CO), 1462, 1383 cm^{-1}. MS (EI, 70 eV, 80 °C): m/z 282 (M^+), 155, 141, 113, 99, 97, 81, 71, 69. ^{1}H-NMR δ 1.32 (d, J = 6.3 Hz, 3 H), 2.98 (m, 2 H), 3.25 (dd, J = 5, 10 Hz, 1 H), 3.35 (dd, J = 6.2, 10 Hz, 1 H), 4.02 (q, br, J = 5.5 Hz, 1 H), 4.12 (dd, J = 1.3, 11.3 Hz, 1 H), 4.16 (dd, J = 3.8, 11.3 Hz, 1 H), 5.05 (dt, br, J = 1.3, 3.8 Hz, 1 H). ^{13}C-NMR δ 8.6 (t), 11.3 (q), 36.8 (d), 49.1 (d), 72.0 (t), 77.8 (d), 82.7 (d), 177.5 (s). Anal. Calcd: C, 34.06; H, 3.93. Found: C, 33.85; H, 3.7.

(3*S*,3a*R*,4*R*,6a*S*)-3-Chloro-4-(iodomethyl)furo[3,4-*b*]furan-2-one (18h). Reaction with lactone **8h** (0.16 g, 0.91 mmol) following the standard procedure, reaction time: 4 h. Chromatography: EtOAc/hexanes 1:2, R_f = 0. 22. Yield: 233 mg (85%), mp 162 °C. $[\alpha]^{23}_D$ −2.1 (c = 2.3 in $CHCl_3$). IR (KBr, film) 1774 (CO), 1416, 1371 cm^{-1}. MS (EI, 70 eV, 100 °C): m/z 302 (M^+), 175, 161, 117, 97, 91, 88, 81, 69. ^{1}H-NMR δ 3.24 (td, br, J = 3.8, 8.8 Hz, 1 H), 3.4 (dd, J = 5, 11.3 Hz, 1 H), 3.58 (dd, J = 2.5, 11.3 Hz, 1 H), 4.12 (m, 1 H), 4.2 (d, br, J = 11.3 Hz, 1 H), 4.34 (dd, J = 3.8, 11.3 Hz, 1 H), 4.9 (d, J = 8.8 Hz, 1 H), 5.16 (t, br, J = 3.8 Hz, 1 H). ^{13}C-NMR δ 9.1 (t), 49.8 (d), 53.2 (d), 72.9 (t), 78.5 (d), 82.6 (d), 170.1 (s). Anal. Calcd: C, 27.79; H, 2.67. Found: C, 27.51; H, 2.44.

(3*S*,3a*R*,4*R*,6a*S*) 3-(Benzyloxy)-4-(iodomethyl)furo[3,4-*b*]furan-2-one (18i). Reaction with lactone **8i** (0.15 g, 0.6 mmol) following the standard procedure, reaction time: 1 h. Chromatography: EtOAc/hexanes 1:4, R_f = 0. 11. Yield: 212 mg (94%), mp 123 °C. $[\alpha]^{23}_D$ −50.6 (c = 1 in $CHCl_3$). IR (KBr, film) 3062, 3035, 1783 (CO), 1455, 1427 cm^{-1}. MS (EI, 70 eV, 120 °C): m/z 374 (M^+), 268, 141, 107, 97, 91. ^{1}H-NMR δ 3.02 (q, br, J = 6.3 Hz, 1 H), 3.27 (dd, J = 4.3, 11 Hz, 1 H), 3.43 (dd, J = 5, 11 Hz, 1 H), 4.1 (d, J = 11.3 Hz, 1 H), 4.21 (m, 1 H), 4.45 (d, J = 8.8 Hz, 1 H), 4.83 (d, J = 11.5 Hz, 1 H), 4.97 (t, br, J = 3.8 Hz, 1 H), 5.05 (d, J = 11.5 Hz, 1 H), 7.38 (m, 5 H). ^{13}C-NMR δ 9.7 (t), 48.6 (d), 72.7 (t), 72.9 (t), 73.4 (d), 76.9 (d), 81.3 (d), 127.9 (d), 128.2 (d), 128.6 (d), 136.5 (s), 173.5 (s). Anal. Calcd: C, 44.94; H, 4.04. Found: C, 44.76; H, 3.9.

(1′*R*,3*S*,4*R*,5*S*)-4-Ethenyl-5-(1-hydroxypentyl)-3-methyl-2(3*H*)-furanone (20) and (1′*S*,3*S*,4*R*,5*S*)-4-Ethenyl-5-(1-hydroxypentyl)-3-methyl-2(3*H*)-furanone (21).

Swern Oxidation. Under Ar, oxalyl chloride (0.26 mL, 391 mg, 3.08 mmol) was dissolved in dry THF (25 mL) at −60 °C. Dry DMSO (0.24 mL, 265 mg, 3.39 mmol) in dry THF (5 mL) was slowly injected with stirring. The reaction temperature was maintained at −55 °C to −60 °C for 1 h, and then **8b** (350 mg, 2.24 mmol) in dry THF (5 mL) was added. After stirring for 1 h at −60 °C to −65 °C, dry Et_3N (0.89 mL, 648 mg, 6.41 mmol) was injected slowly, and the white precipitate of Et_3N·HCl occurred. After stirring for 1 h at −55 °C to −60 °C, the mixture was allowed to warm up to rt. Careful TLC monitoring indicated the completion of the oxidation after about 30 min (R_f aldehyde = 0.17, EtOAc/hexanes, 1:1). The mixture was then immediately cooled to −70 °C.

Grignard Reaction. To the *in situ* generated aldehyde was injected a freshly prepared 0.5 M solution of *n*BuMgBr (1.6 equiv, 7.3 mL, 3.64 mmol) in dry THF. After a reaction time of about 4 h at −70 °C, saturated aqueous NH_4Cl (40 mL) was added. The aqueous layer was extracted with Et_2O (5 × 20 mL), and the combined organic layers were washed with brine and dried ($MgSO_4$). Evaporation of the solvent and chromatographic purification on silica gel (EtOAc/hexanes 1:3) gave **20** and **21**: 419 mg (88%, R_f = 1.8). Separation of the diastereomeric lactones **20** and **21** (ratio: 1:10) *via* preparative HPLC: Eluent: 5% 2-propanol in hexanes. Minor diastereomer lactone **20**: retention time 2.21 min, 38 mg (8%), mp 107 °C. $[\alpha]^{23}_D$ 43.5 (c = 0.8 in $CHCl_3$). IR (KBr, film) 3473 (br, OH), 3081, 1777 (CO), 1456 cm^{-1}. MS (EI, 70 eV, 60 °C): m/z 212 (M^+), 183, 170, 156, 152, 126, 111, 98, 87, 81, 70, 68. ^{1}H-NMR δ 0.92 (t, J = 7 Hz, 3 H), 1.1 (d, J = 7 Hz, 3 H), 1.33 (m, 3 H), 1.5 (m, 2 H), 1.78 (m, 1 H), 1.94, (s, br, 1 H, OH), 2.86 (qi, J = 7 Hz, 1 H), 3.2 (ddd, J = 4.5, 7, 10 Hz, 1 H), 3.68 (dt, br, J = 1.3, 8.3 Hz, 1 H), 4.11 (dd, J = 4.5, 8.8 Hz, 1 H), 5.1 (dd, J = 2, 16.3 Hz, 1 H), 5.14 (dd, J = 2, 10 Hz, 1 H), 5.69 (td, J = 10, 16.3 Hz, 1 H). ^{13}C-NMR δ 10.4 (q), 13.9 (q), 22.5 (t), 27.1 (t), 33.6 (t), 39.6 (d), 47.9 (d), 69.3 (d), 82.4 (d), 120.5 (t), 131.9 (d), 178.3 (s). Anal. Calcd: C, 67.89; H, 9.5. Found: C, 67.54; H, 9.19. Major diastereomer lactone **21**: retention time 2.59 min, 381 mg (80%), mp 65−66 °C. $[\alpha]^{23}_D$ −2.2 (c = 1 in $CHCl_3$). IR (KBr, film) 3327 (br, OH), 3081, 1776 (CO), 1469 cm^{-1}. MS (EI, 70 eV, 60 °C): m/z 212 (M^+), 183, 170, 156, 139, 126, 111, 87, 81, 70. ^{1}H-NMR δ 0.92 (t, J = 7 Hz, 3 H), 1.13 (d, J = 7 Hz, 3 H), 1.35 (m, 4 H), 1.5 (m, 2 H), 2.29, (s, br, 1 H, OH), 2.91 (qi, J = 7 Hz, 1 H), 3.06 (ddd, J = 4.8, 7, 10 Hz, 1 H), 3.7 (t, br, J = 7.8 Hz, 1 H), 4.21 (dd, J = 4.8, 7.8 Hz, 1 H), 5.2 (dd, J = 1, 17 Hz, 1 H), 5.29 (dd, J = 1, 10 Hz, 1 H), 5.59 (td, J = 10, 17 Hz, 1 H). ^{13}C-NMR δ 10.4 (q), 13.8 (q), 26.3 (t), 26.9 (t), 30.1 (t), 40.1 (d), 47.7 (d), 70.3 (d), 84.6 (d), 120.4 (t), 130.6 (d), 178.0 (s). Anal. Calcd: C, 67.89; H, 9.5. Found: C, 67.8; H, 9.43.

***rel*-(3*S*,3a*R*,6*S*,6a*S*)-6-Butyl-3-methyltetrahydrofuro-[3,4-*b*]furan-2,4(3*H*, 3a*H*)-dione [(−)-3-*epi*-dihydrocanadensolide (22)]:**

Ozonlysis. The hydroxy lactone **21** (150 mg, 0.71 mmol) in MeOH (12 mL) was cooled to −78 °C. A stream of O_3/O_2 was bubbled through the reaction mixture until the blue color of unreacted O_3 appeared (about 5 min). Reductive workup with PPh_3 (371 mg, 1.41 mmol) led after 1 h stirring at −78 °C and 1 h stirring at rt to a solution of the corresponding lactol (R_f = 0.33, EtOAc/hexanes 1:1). Then, the solvent was removed and the crude material was vacuum dried.

PCC Oxidation. The crude lactol in CH_2Cl_2 (15 mL) was poured into a suspension of pyridinium chlorochromate (PCC, 2.41 g, 11.2 mmol) in dry CH_2Cl_2 (30 mL). The mixture was stirred at rt, until the lactol disappeared after TLC control (about 6 h, the detection of the product is quite difficult!). Then, the solution was filtered through 10 cm silica gel (CH_2Cl_2) to remove the chromium salts. Evaporation of the solvent gave a white solid material containing **22** and PPh_3O. The bislactone **22** was isolated after chromatography on silica gel (EtOAc/hexanes 1:2, R_f = 0.1). Purification *via* preparative HPLC (eluent: 10% 2-propanol in hexanes): retention time 5.77 min, yield 109 mg (73%), mp 70 °C. $[\alpha]^{23}_D$ −20.6 (c = 1.3 in $CHCl_3$). IR (KBr, film) 1783 and 1764 (CO), 1458 cm^{-1}. MS (EI, 70 eV, 100 °C): m/z 212 (M^+), 166, 155, 140, 125, 112, 98, 69. ^{1}H-NMR δ 0.96 (t, J = 5.5 Hz, 3 H), 1.44 (m, 4 H), 1.5 (d, J = 7.5 Hz, 3 H), 1.88 (m, 2 H), 3.1 (dq, J = 7.5, 10 Hz, 1 H), 3.5 (dd, J = 5.3, 10 Hz, 1 H), 4.55 (dt, br, J = 3.8, 7 Hz, 1 H), 5.06 (dd, J = 3.8, 5.3 Hz, 1 H). ^{13}C-NMR δ 10.7 (q), 13.7 (q), 22.2 (t), 27.3 (t), 28.3 (t), 36.5 (d), 44.5 (d), 78.0 (d), 81.4 (d), 172.2 (s), 176.2 (s). Anal. Calcd: C, 62.25; H, 7.6. Found: C, 62.22; H, 7.51.

(1′*S*,3*R*,4*R*,5*S*)-4-Ethenyl-5-(1-hydroxypentyl)-3-methyl-2(3*H*)-furanone (23). Under Ar, **21** (160 mg, 0.75 mmol) was dissolved in dry THF (11 mL) and KO*t*Bu (43 mg, 0.38 mmol) was added. The mixture was stirred at rt for 1.5 h, and then 1 N aqueous $NaHSO_4$ (2 mL) was injected. After neutralizing with saturated aqueous $NaHCO_3$, the aqueous layer was extracted with Et_2O (5 × 15 mL). The combined organic layers were dried ($MgSO_4$), the solvent was removed, and the crude material was purified via column chromatography (EtOAc/hexanes 1:2, R_f = 0.24). Purification via preparative HPLC (eluent: 2% 2-propanol in hexanes): retention time 2.2 min, yield 141 mg (88%). $[\alpha]^{23}_D$ 84.1 (c = 2.4 in

$CHCl_3$). IR (KBr, film) 3450 (br, OH), 1759 (CO), 1446 cm^{-1}. MS (EI, 70 eV, 100 °C): *m/z* 212 (M^+), 156, 126, 111, 97, 87, 81, 70. ^{1}H-NMR δ 0.84 (t, J = 6.3 Hz, 3 H), 1.07 (d, J = 6 Hz, 3 H), 1.26 (m, 4 H), 1.58 (m, 2 H), 2.78 (m, br, 3 H), 3.65 (q, br, J = 6.3 Hz, 1 H), 4.26 (d, br, J = 7.5 Hz, 1 H), 5.12 (d, J = 11.3 Hz, 1 H), 5.16 (d, J = 16.3 Hz, 1 H), 5.92 (m, 1 H). ^{13}C-NMR δ 13.7 (q), 13.8 (q), 22.4 (t), 27.8 (t), 33.3 (t), 39.2 (d), 51.6 (d), 70.7 (d), 82.2 (d), 119.4 (t), 134.6 (d), 180.3 (s). Anal. Calcd: C, 67.89; H, 9.5. Found: C, 67.81; H, 9.39.

***rel*-(3*R*,3a*R*,6*S*,6a*S*) 6-Butyl-3-methyltetrahydrofuro-[3,4-*b*]furan-2,4(3*H*,3a*H*)-dione [(+)-dihydrocanadensolide (24)].** Oxidation sequence starting from hydroxy lactone **23** (120 mg, 0.56 mmol) using conditions as described for bislactone **22**. Chromatography: EtOAc/hexanes 1:2, R_f = 0.14. Purification via preparative HPLC (eluent: 12% 2-propanol in hexanes): retention time 2.76 min, yield 96 mg (80%), mp 93−94 °C, lit. 94 °C). $[\alpha]^{23}_D$ 30.3 (c = 1.9 in $CHCl_3$), 30 (c = 1.7 in MeOH), (lit. 30 c = 1.0 in MeOH). IR (KBr, film) 1767 (CO), 1468 cm^{-1}. MS (EI, 70 eV, 100 °C): *m/z* 212 (M^+), 166, 155, 139, 125, 112, 98, 69. ^{1}H-NMR δ 0.92 (t, J = 7 Hz, 3 H), 1.4 (m, 4 H), 1.44 (d, J = 7.5 Hz, 3 H), 1.84 (m, 2 H), 3.04 (q, br, J = 7.5 Hz, 1 H), 3.15 (d, br, J = 6.3 Hz, 1 H), 4.53 (dt, J = 3.8, 7 Hz, 1 H), 5.09 (dd, J = 3.8, 6.3 Hz, 1 H). ^{13}C-NMR δ 13.7 (q), 16.8 (q), 22.2 (t), 27.3 (t), 28.3 (t), 38.2 (d), 48.8 (d), 78.4 (d), 82.2 (d), 174.8 (s), 176.8 (s). Anal. Calcd: C, 62.25; H, 7.6. Found: C, 62. 2; H, 7.51.

Acknowledgment. I thank the DFG and the FNK for support of this research.

Supporting Information Available: NOEDS data for the compounds **8**−**11**, **14**, **15**, **18**, **22** and ^{13}C NMR spectra for the compounds **5h**, **5/7i**, **6f**, **10f** (7 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

JO9600464