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Preparation of 2,4-Disubstituted Cyclopentenones by Enantioselective Iridium-Catalyzed Allylic Alkylation: Synthesis of 2′-Methylcarbovir and *TEI-9826*

Pierre Dübon, Mathias Schelwies, and Günter Helmchen*[a]

Dedicated to Professor Volker Jäger on the occasion of his 65th birthday

Abstract: A broadly applicable synthesis of chiral 2- or 2,4-substituted cyclopent-2-enones has been developed by combining asymmetric iridium-catalyzed allylic alkylation reactions and ruthenium-catalyzed ring-closing metathesis. Enantiomeric excesses (*ee* values) in the range of 95–99% *ee* have been achieved. This method offers a straightforward access to biologically active prostaglandins of the PGA type. As an example, an enantioselective synthesis of the prostaglandin-analogue 13,14-dihydro-15-deoxy-Δ^7-prostaglandin-A1-methyl ester (*TEI-9826*) has been carried out. Furthermore, the carbonucleoside 2′-methylcarbovir has been prepared from O-protected 4-hydroxymethyl-2-methyl-cyclopent-2-enone by Pd-catalyzed allylic amination.

Keywords: allylic alkylation · carbocyclic nucleosides · cyclopentenones · iridium · phosphoramidites

Introduction

Many natural products and pharmaceuticals containing a cyclopentane moiety show interesting biological activity. For example, alkylidene cyclopentenones, such as the prostaglandins Δ^7-PGA_1 methyl ester or 15-deoxy-$\Delta^{12,14}$-PGJ_2 (Figure 1), display anti-inflammatory, antiviral or antitumoral activities.[1] Stereoselective synthesis of these compounds remains a topic of active investigation in organic chemistry.[2]

Recently, we have communicated a new enantioselective method, which offers a straightforward access to 4- and 2,4-disubstituted cyclopentenones.[3] These compounds are of special interest as intermediates for the synthesis of 2,4-disubstituted cyclopentenones such as phomapentenone A or of 2-substituted carbocyclic nucleosides, as will be illustrated later.[4] The simpler 4-substituted cyclopentenones, which are also accessible by using the reported method, can serve as precursors in the synthesis of the cyclopentenones that are shown in Figure 1. Further functionalization of a 2,4-disubstituted cyclopentenone can be accomplished at the 3-position by reaction with a nucleophile or at the 5-position by reaction with an electrophile (Scheme 1).[5]

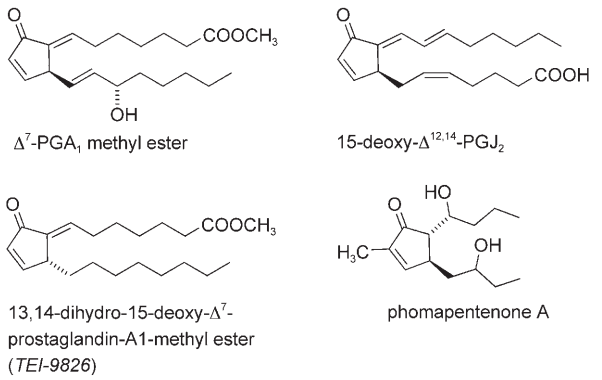
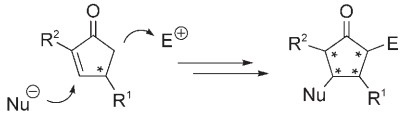


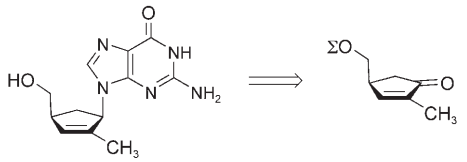
Figure 1. Examples of biologically active cyclopentenones.



Scheme 1. Possibilities for the functionalization of 2,4-disubstituted cyclopentenones.

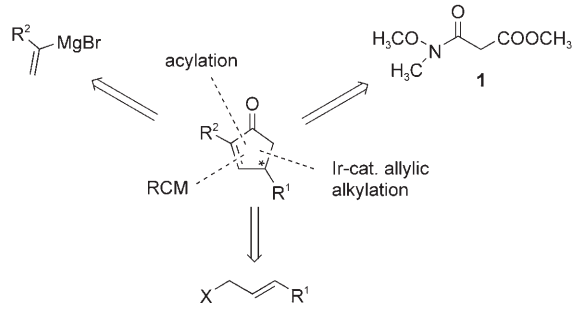
[a] P. Dübon, M. Schelwies, Prof. Dr. G. Helmchen
Organisch-Chemisches Institut der Universität Heidelberg
Im Neuenheimer Feld 270, 69120 Heidelberg (Germany)
Fax: (+49) 6221-544205
E-mail: g.helmchen@oci.uni-heidelberg.de

Herein, we present applications of our method in the syntheses of the prostaglandin analogue *TEI-9826* (Figure 1) and the carbocyclic nucleoside 2′-methylcarbovir. *TEI-9826* is available by aldol condensation from 4-*n*-octyl-cyclopentenone; this compound was chosen to demonstrate the adaptability of the method to the synthesis of prostaglandins. The targeted carbonucleoside was accessed from a 2,4-disubstituted cyclopentenone (Scheme 2).



Scheme 2. A cyclopentenone as a precursor for 2′-methylcarbovir.

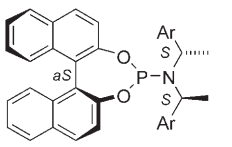
Our synthesis of cyclopentenones is schematically described in Scheme 3, and it involves the following concepts: 1) The chirality center C-4 is constructed with high enantioselectivity by iridium-catalyzed asymmetric allylic alkylation[6] by using the enolate of the Weinreb-type amide **1** as a novel nucleophile.[7] 2) Demethoxycarbonylation and a subsequent acylation by addition of an alkenylmagnesium halide yields a second olefinic moiety. 3) The cyclopentenone is prepared by ring-closing metathesis (RCM).[8] The combination of an allylic substitution and a RCM reaction has already proven to be a very powerful tool in natural-product synthesis.[9]



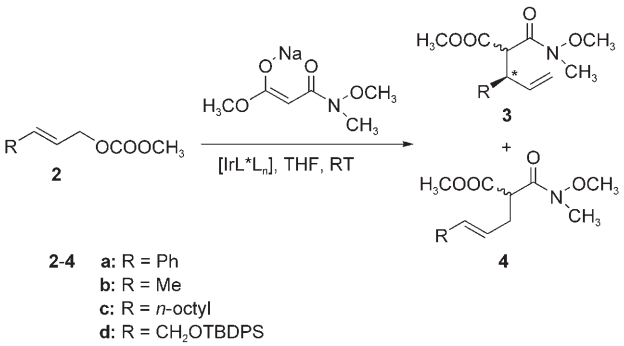
Scheme 3. Retrosynthetic concept.

Results and Discussion

Iridium-catalyzed allylic alkylation: This reaction was introduced in 1997. Today enantioselectivities >90% *ee* (*ee* = enantiomeric excess) can be achieved routinely.[6] The commonly applied catalyst is prepared from a mixture of $[IrCl(cod)]_2$ (cod = 1,5-cyclooctadiene) and a chiral phosphoramidite by reaction with base, which effects C–H activation. The phosphoramidite ligands used here (**L1** and **L2**) were introduced by Feringa[10] and Alexakis.[11]



L1: Ar = Ph
L2: Ar = 2-$(OCH_3)C_6H_4$



2-4 **a:** R = Ph
b: R = Me
c: R = *n*-octyl
d: R = $CH_2OTBDPS$

Scheme 4. Allylic substitution by using a malonic amide of the Weinreb type as a pronucleophile.

The sodium enolate of the Weinreb-type amide **1** was employed as pronucleophile (Scheme 4). Reaction conditions typical for malonates were used (conditions D according to reference [6a]). If not otherwise stated, the reactions were carried out with 2 mol% of $[IrCl(cod)]_2$ in combination with the ligands **L1** and **L2**. Recently reported salt-free conditions, which gave excellent results for malonates,[12] were not suitable for the malonic amide **1**, which is expected to be less acidic than a malonic ester. The allylic carbonates **2a–d** were prepared by standard procedures; amide **1** was available in a single step by reaction of methyl 3-chloro-3-oxopropionate with *N*,*O*-dimethylhydroxylamine hydrochloride/triethylamine.

Table 1. Iridium-catalyzed allylic alkylation of carbonates **2a–d** with Weinreb-type amide **1** according to Scheme 4.

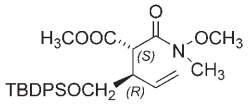
Entry	Substrate	L*	*t* [h][a]	Yield **3+4** [%][b]	**3**/**4**[c]	*ee*[d] [%](absolute configuration)
1	**2a**	**L1**	1	89	>98:2	96 (*R*)
2[e]	**2a**	**L2**	0.5	88	>98:2	98 (*R*)
3[e]	**2b**[f]	**L1**	3	83	94:6	95 (*R*)
4	**2b**[f]	**L2**	2	76	94:6	95 (*R*)
5	**2c**[f]	**L1**	18	89	83:17	96 (*R*)
6	**2c**[f]	**L2**	5.5	62	84:16	99 (*R*)
7[e]	**2d**	**L1**	6	85	86:14	97.5 (*R*)
8	**2d**	**L2**	1.5	69	66:34	98 (*R*)

[a] Reaction time. [b] Yield of the isolated mixture of the regioisomeric products **3** and **4**. [c] Determined by ^1H NMR spectroscopy. [d] Determined by HPLC on a chiral column. In all cases the branched compounds **3** were obtained as 1:1 mixtures of diastereoisomers. All absolute configurations refer to the starred (*) chiral center in Scheme 4. Compounds **4** were racemic. [e] 2 mol% of iridium was used. [f] The substrate contained approximately 3% of the *Z* diastereoisomer.[15]

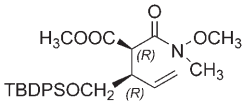
The results obtained for the allylic substitutions depicted in Scheme 4 are displayed in Table 1. The reactions generally proceeded in good yield and with high enantio- and regioselectivity. Selectivities were similar to those obtained with dimethyl sodiomalonate, that is, the enantiomeric excesses were found to be in the range 95–99% *ee* and the regioselectivities in the range of 83:17 to 98:2. An exception is the reaction with substrate **2d**, which proceeded with low regioselectivity (70:30) upon the use of ligand **L2**, as was previ-

ously found with malonates as nucleophiles;[6f] however, in combination with the less bulky ligand **L1**, selectivities were significantly better. Regioselectivities were determined by ^{1}H NMR spectroscopy; the requisite pure linear regioisomers **4** were prepared by Pd-catalyzed allylic substitution by using standard procedures. The enantioselectivities of **3a–d** were determined by HPLC on a Daicel column.

The branched products **3** were obtained as 1:1 mixtures of diastereoisomers. Their separation was not possible, except in the case of malonic amide **3d** of which both diastereoisomers were sufficiently stable for separation by HPLC.



(+)-(2*S*,3*R*)-**3d**



(+)-(2*R*,3*R*)-**3d**

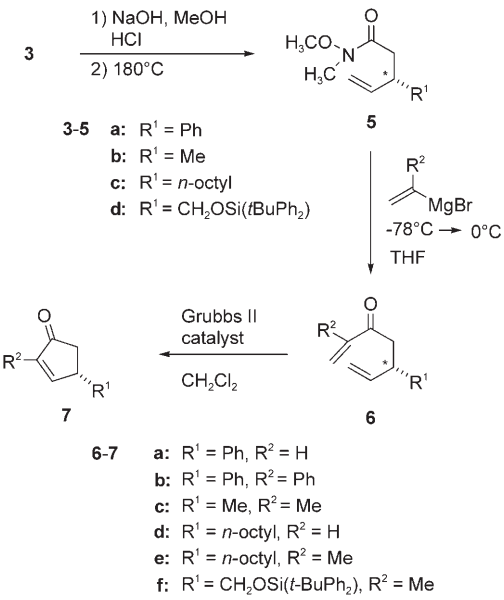
The TBDPS-protected product (+)-(2*R*,3*R*)-**3d** was crystalline and its absolute and relative configuration was determined by X-ray crystal structure analysis.[13] For the other products, absolute configurations were assigned according to a rule that has been found to hold without exception so far.[6a,14]

Preparation of the 2,4-disubstituted cyclopentenones 7–12: Mixtures of the regioisomers **3** and **4** were converted into the 2,4-disubstituted cyclopentenones in three steps (Scheme 5, Table 2) as follows: Demethoxycarbonylation of **3** and **4** by saponification/decarboxylation gave amides **5** in yields of >80%. In the following step, amides **5** were converted into enones **6** by Grignard reactions under previously described conditions.[16] Finally, RCM with Grubbs II catalyst[17] yielded 2,4-disubstituted cyclopentenones **7a–f**. In this step, impurities resulting from the linear regioisomers **4** were easily removed by column chromatography. After RCM, the enantiomeric excesses were checked by HPLC again and no racemization was found. With the exception of the extremely volatile enone **7c**, the overall yields exceeded 50%.

Enone **7c** commands particular interest because it has been identified as a volatile flavor ingredient of dried fish.[18] Both enantiomers were prepared and their olfactory properties characterized (Table 3).

Synthesis of the prostaglandin analogue *TEI-9826* (10): The prostaglandin analogue *TEI-9826* (**10**) shows activity against cisplatin-resistant tumors.[19] Furthermore, a new antitumor mechanism has been proposed for this compound.[20] Syntheses of the racemate and of one of the pure enantiomers (98% *ee*), obtained by resolution, have been described.[21]

The transformation of cyclopentenone **7d** into *TEI-9826* has already been described by Monneret et al.[21c] However, no experimental details have been published. Accordingly, we repeated this work with (−)-(*S*)-**7d** as described in



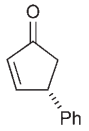
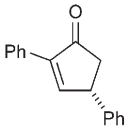
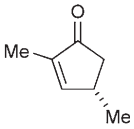
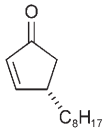
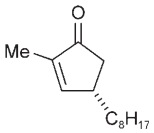
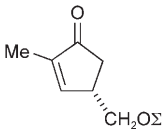
Scheme 5. Conversion of amides **3** to chiral cyclopentenones **7a–f**.

Scheme 6. LDA (LDA = lithium diisopropylamide) was used as the base[22] for the aldol reaction of **7d** with methyl 6-formylhexanoate to yield the *anti* aldol product **8** in 58% yield. The relative configuration of **8** was determined by comparison of coupling constants between H_a and H_b (8.4 Hz) with values reported for similar compounds by Kobayashi et al.[22] Coupling constants of $J_{a,b} \approx 3$ and 8.4–9.6 Hz are typical for *syn* and *anti* aldol products, respectively. For the subsequent elimination, a procedure of Kobayashi et al. was applied,[22] which involved conversion of the alcohol **8** to the mesylate **9**, which was subsequently treated with neutral Al_2O_3 to give *TEI-9826* (**10**) in 77% yield over two steps. This kind of elimination is known as a *syn*-specific reaction and yielded the (*E*)-olefin.[23] The overall yield of *TEI-9826* (**10**) from **7d** was 45%.

Synthesis of 2′-methylcarbovir: Carbonucleosides often display conformers different from those of the corresponding nucleosides. One reason is the lack of an anomeric effect. As a remedy for this problem, medicinal chemists are devising carbocyclic nucleosides that are locked in conformations which are considered to be important for biological activity.[24] 2′-Substituted carbocyclic nucleosides constitute one class of conformationally locked compounds, and accordingly are interesting targets for synthesis.[25] The 2,4-disubstituted cyclopentenone **7f** appears to be well suited as a precursor for these compounds. We have tested this approach by carrying out an asymmetric synthesis of 2′-methylcarbovir, a compound previously synthesized by Crimmins et al.[25b] who used an auxiliary-controlled aldol reaction and RCM as key steps.

Our synthesis of 2′-methylcarbovir from **7f** required five steps and is described in Schemes 7 and 8. In the first step, (*S*)-**7f** was reduced with DIBAL (diisobutylaluminum hydride) to give the *cis*-alcohol **11** accompanied by a small

Table 2. Synthesis of cyclopentenones according to Scheme 5.

Entry	Starting material	R^1	R^2[c]	Yield [%][a]	Product	*ee* [%][b]
1	(*R*)-**3a**	Ph	H	66	 (-)-(*S*)-**7a**	97
2	(*R*)-**3a**	Ph	Ph	55	 (-)-(*S*)-**7b**	96
3	(*R*)-**3b**	Me	Me	44[c]	 (-)-(*S*)-**7c**	95
4	(*R*)-**3c**	*n*-octyl	H	56	 (-)-(*S*)-**7d**	96
5	(*R*)-**3c**	*n*-octyl	Me	50	 (-)-(*S*)-**7e**	n.d.[d]
6[e]	(*R*)-**3d**	$CH_2O\Sigma$	Me	56	 (-)-(*S*)-**7f** $\Sigma = Si(t\mathrm{BuPh}_2)$	98

[a] Starting from **3** and **4**. [b] Determined by HPLC on a chiral column; in each case both enantiomers were prepared. [c] Volatile compound. [d] n.d. = not determined. [e] Saponification with LiOH.

Table 3. Olfactory characterization of (*S*)- and (*R*)-**7c**.[a]

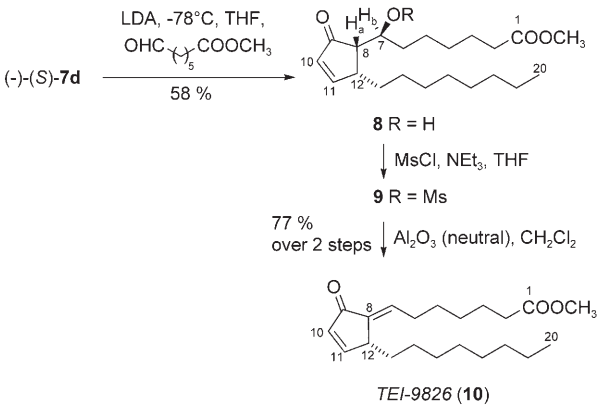
Substance	Fragrance description
(−)(*S*)-**7c** (95.5% *ee*)	Ethereal, herbaceous and nutty in the direction of hazelnut, sweeter in tonality but also significantly weaker in strength compared with its enantiomer
(+)(*R*)-**7c** (93% *ee*)	More intense in odor strength compared with its enantiomer, and more pronounced tobacco and leathery character with haylike facets, besides also ethereal, herbaceous, and sweet

[a] Carried out by Givaudan SA (Dr. P. Kraft), Dübendorf, Switzerland.

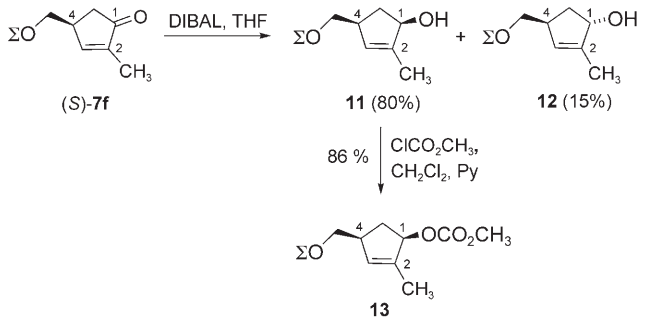
amount of the *trans*-diastereoisomer **12**. Pure **11** and **12** were obtained by column chromatography in 80 and 15% yields, respectively. Alcohol **11** was transformed into the carbonate **13** (86%) in the standard manner.

A Pd-catalyzed allylic amination was planned as the next step (Scheme 8). This is a standard step in carbonucleoside synthesis that has been carried out often before. However, it usually gives rise to mixtures of isomers: 1) The formation of regioisomers with respect to N-9 and N-7 of the purine has been observed frequently with various nucleobases, such as 2-amino-6-chloropurine, which was used here.[25a,b,26] 2) The formation of isomers with respect to the cyclopentene moiety has also been described. *Cis* and *trans* isomers[27] and 1,2- and 1,4-regioisomers have been encountered.[27,28]

In our synthesis, the allylic carbonate **13** was reacted with 2-amino-6-chloropurine. The regioisomers **14** and **15** were formed in an 86:14 ratio. The mixture was treated with pyridine·HF to effect deprotection, and the resultant alcohols **16** and **17** were separated. The relative and absolute configurations of both isomers were confirmed by X-ray crystal structure analysis (see below).[13] The final transformation of **16** into 2′-methylcarbovir (**18**) by treatment with NaOH proceeded in 82% yield. NMR spectroscopic data of **18** were in accordance with data published by Crimmins et al.[25b] However, the op-



Scheme 6. Conversion of cyclopentenone **7d** to prostaglandin analogue *TEI-9826* (**10**). Ms = methanesulfonyl.



Scheme 7. Synthesis of carbonate **13** ($\Sigma = Si(t\mathrm{BuPh}_2)$, Py = pyridine).

tical rotation of $[\alpha]_D^{20} = +10.4$ ($c = 0.11$ in MeOH) is completely different from the reported value. To reliably determine the *ee* and to reconfirm the optical rotation measured by us, the enantiomer of **18** was also prepared. The enantiomeric excess of **18** was determined to be 97.5% *ee*; accordingly, our synthesis had proceeded without racemization.

Compound **16** displays a pseudoequatorial conformation in the solid state (Figure 2), which is very similar to that of the cyclopentene moiety of Carbovir.[29] However, the structures differ considerably with respect to the torsion angle around the C-1′–N-9 bond.

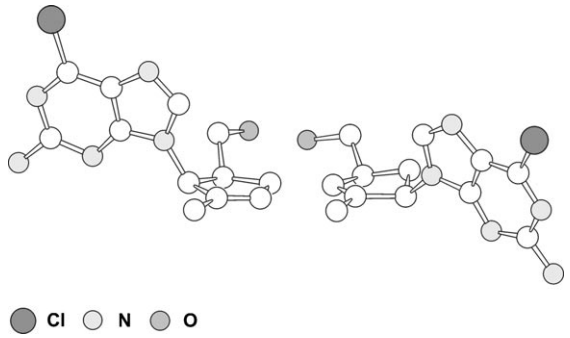


Figure 2. X-ray crystal structures of the isomers **16** (right) and **17** (left).

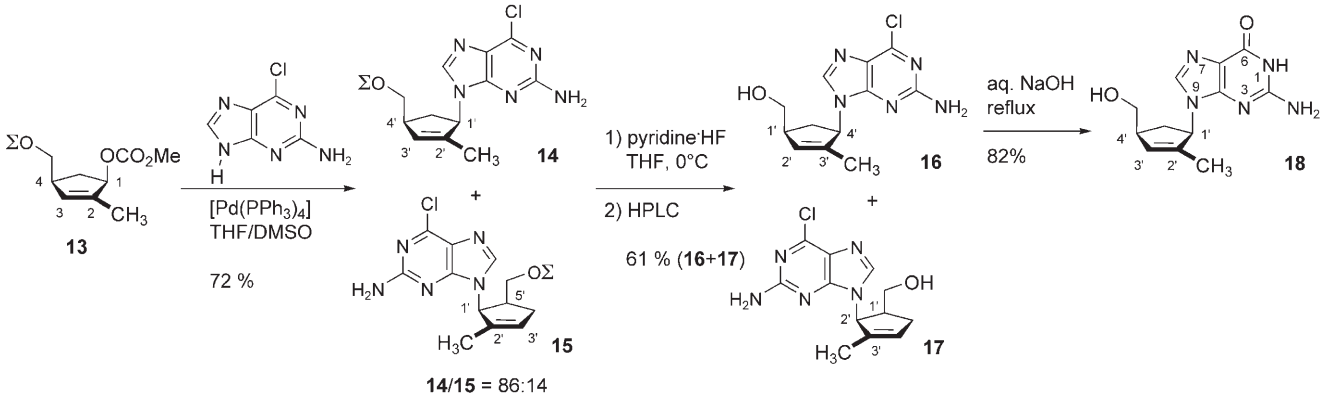
Conclusion

We have presented a short and flexible route to 2,4-disubstituted cyclopentenones. Key steps were an iridium-catalyzed allylic substitution and a ruthenium-catalyzed ring-closing metathesis reaction. Cyclopentenones **7a–f** were synthesized in excellent enantiomeric excesses and in good yields. The first asymmetric synthesis of 2,4-dimethylcyclopentenone **7c** and the flavor description of both enantiomers of this compound are reported. Furthermore, the prostaglandin analogue *TEI-9826* and the carbonucleoside 2′-Methylcarbovir were synthesized by starting from cyclopentones **7d** and **7f**, respectively.

Experimental Section

General: ^{1}H NMR spectra were recorded at RT on Bruker AC-300 (300 MHz) or Bruker Avance 500 (500 MHz) spectrometers. Chemical shifts are reported in δ units relative to $CHCl_3$ ($\delta_H = 7.26$ ppm). ^{13}C NMR spectra were recorded on Bruker AC-300 (75 MHz) or Bruker Avance 500 (125 MHz) spectrometers. Chemical shifts are reported in δ units relative to $CHCl_3$ ($\delta_C = 77.16$ ppm (central line of the triplet)). The following abbreviations were used throughout: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet. The assignments of signals for compounds **2–18** were confirmed by ^{1}H,^{1}H-COSY, ^{1}H,^{13}C-COSY and DEPT spectra. Optical rotations were measured with a Perkin–Elmer 341 Polarimeter in a 1 dm thermostated cuvette by using a mercury lamp. Concentration *c* is given in g per 100 mL. HRMS were recorded on a JEOL JMS-700 instrument. Elemental analyses were carried out at the Organisch-Chemisches Institut, Universität Heidelberg. Enantiomeric excesses were determined by chiral HPLC on a HP 1100 instrument. The following columns from Daicel were used: Chiralpak AD-H (250×4.6 mm, 5 μm) with guard cartridge AD-H (10×4 mm, 5 μm) and Chiralcel OD-H (250×4.6 mm, 5 μm) with guard cartridge OD-H (10×4 mm, 5 μm). For preparative HPLC a Gilson-305 pump coupled with a Knauer UV detector 2600 and a silica-gel column (Latek, 5μ, 21×250 mm) were used.

THF was dried over sodium benzophenone ketyl, and the water content was determined by Karl Fischer titration. 1,5,7-Triazabicyclo[4.4.0]dec-5-ene (TBD) was stored in a dessicator over KOH; alternatively, small amounts were stored under argon in a Schlenk tube. Magnesium turnings used for the preparation of Grignard reagents were activated by addition of a drop of 1,2-dibromoethane. IUPAC names were generated with the program ACD/Lab 6.0 from Advanced Chemistry Development Inc.



Scheme 8. Synthesis of 2′-methylcarbovir from cyclopentene **13**.

Methyl 3-[methoxy(methyl)amino]-3-oxopropanoate (1): A solution of triethylamine (32.59 g, 366.2 mmol) in dry CH_2Cl_2 (55 mL) was added dropwise to a cold (0 °C) solution of methyl 3-chloro-3-oxopropanoate (25.00 g, 183.1 mmol) and *N*,*O*-dimethylhydroxylamine hydrochloride (17.86 g, 183.1 mmol) in dry CH_2Cl_2 (450 mL) under an argon atmosphere. The resulting yellow solution was stirred for 1 h at 0 °C and for 12 h at RT. Conversion was then complete (monitored by TLC), and the mixture was extracted with water (200 mL). The aqueous layer was re-extracted with CH_2Cl_2 (3×200 mL) and the combined organic layers were washed with brine (400 mL), dried over Na_2SO_4, and concentrated in vacuo to give a brown oil as the crude product. Distillation (74 °C, 0.1 mbar) yielded amide **1** (18.9 g, 64 %) as a colorless oil. R_f(**1**) = 0.21 (CH_2Cl_2/methanol 100:1); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.69, 3.66 (2 s, 6 H; OCH_3), 3.46 (s, 2 H; CH_2), 3.17 ppm (s, 3 H; NCH_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 167.8, 167.2 (2 s; C=O), 61.4, 52.3 (2 q; OCH_3), 39.7 (t; CH_2), 32.2 ppm (q; NCH_3); elemental analysis calcd (%) for $C_6H_{11}NO_4$: C 44.72, H 6.88, N 8.69; found: C 44.97, H 7.00, N 8.40.

General procedure 1 (GP1, Ir-catalyzed allylic alkylation): Malonic amide **1** (1.3 mmol) was added dropwise to a stirred suspension of NaH (95 %, 1.3 mmol) in dry THF (4.0 mL) to give solution A. A solution of $[IrCl(cod)]_2$ (13.4 mg, 20.0 μmol) and **L1** or **L2** (40 μmol) in anhydrous THF (1.0 mL, content of water < 50 μg mL^{-1}, Karl Fischer titration) was treated with tetrahydrothiophene (THT) (18 μL, 0.20 mmol) and TBD (11.1 mg, 80.0 μmol), and the mixture was stirred for 2 h under an argon atmosphere. Then, allylic carbonate (1.0 mmol), CuI (38 mg, 0.20 mmol), and solution A were successively added and the mixture was stirred for the time stated in Table 1; conversion was monitored by TLC. After complete conversion had been reached, diethyl ether (5 mL) and saturated NH_4Cl solution (5 mL) were added, and the aqueous phase was extracted with diethyl ether (2×20 mL). The combined organic phases were washed with brine (20 mL), dried over Na_2SO_4, filtered, and concentrated in vacuo. The crude product was analyzed with respect to the ratio of branched and linear products by ^{1}H NMR spectroscopy and then subjected to flash column chromatography (silica, petroleum ether/ethyl acetate).

Methyl (3*R*)-{[methoxy(methyl)amino]carbonyl}-3-phenylpent-4-enoate (3a): **GP1** was carried out with $[IrCl(cod)]_2$ (33.5 mg, 49.9 μmol), (*S*,*S*,*aS*)-**L2** (59.9 mg, 0.100 mmol), TBD (42 mg, 0.30 mmol), THT (44 μL, 0.50 mmol), CuI (95 mg, 0.50 mmol), NaH (95 %, 139 mg, 5.50 mmol), **2a** (961 mg, 5 mmol), **1** (886 mg, 5.50 mmol) and dry THF (15 mL). Complete conversion was reached after the reaction mixture had been stirred for 0.5 h at RT (monitored by TLC R_f(**2a**) = 0.47 (petroleum ether/ethyl acetate 3:1)) and a workup was carried out. ^{1}H NMR spectroscopic analysis of the crude product was used for the determination of the ratio of the regioisomers (**3a**/**4a** > 98:2). The crude product was subjected to flash chromatography on silica (petroleum ether/ethyl acetate 4:1) to yield **3a** (1.22 g, 88 %) containing < 2 % of **4a**, as a colorless oil. R_f(**3a**) = 0.12 (petroleum ether/ethyl acetate 3:1); ^{1}H NMR (300 MHz, $CDCl_3$): mixture of branched diastereoisomers in a ratio of 51:49; δ = 7.29–7.14 (m, 5 H; 2×Ar), 6.02–5.93 (m, 1 H; 2×C*H*=CH$_2$), 5.13–5.03 (m, 2 H; 2×CH=C*H*$_2$), 4.36–4.33 (m, 1 H; 2×CH), 4.21–4.18 (m, 1 H; 2×CH), 3.72 (s, 3 H; $COOCH_3$), 3.70 (s, 3 H; $NOCH_3$), 3.59 (s, 3 H; $COOCH_3$), 3.44 (s, 3 H; $NOCH_3$), 3.19 (s, 3 H; NCH_3), 2.93 ppm (s, 3 H; NCH_3); ^{13}C NMR (75 MHz, $CDCl_3$): mixture of branched diastereoisomers; δ = 168.7, 168.5, 168.4, 168.0 (4 s; C=O), 140.7, 140.6, 138.6, 138.4 (4 s; Ar), 128.6, 128.6, 128.3, 128.2, 127.0, 126.9 (6 d; Ar), 116.4 (t; 2×CH=*C*H$_2$), 61.7, 61.6 (2 q; $NOCH_3$), 53.4, 53.1 (2 d; CH), 52.5, 52.3 (2 q; $COOCH_3$), 49.4, 49.4 (2 d; CH), 32.6, 32.4 ppm (2 q; NCH_3); elemental analysis calcd (%) for $C_{15}H_{19}NO_4$: C 64.97, H 6.91, N 5.05; found: C 64.85, H 6.93, N 5.12; HPLC (Daicel AD-H column, *n*-hexane/*i*PrOH 95:5, 20 °C, 210 nm): t_r((3*S*)-**3a**) = 28/37, t_r((3*R*)-**3a**) = 33/47 min, 98 % *ee* for both diastereoisomers.

Methyl (3*R*)-2-{[methoxy(methyl)amino]carbonyl}-3-methylpent-4-enoate (3b): **GP1** was carried out with $[IrCl(cod)]_2$ (20.2 mg, 30.0 μmol), (*S*,*S*,*aS*)-**L2** (36.0 mg, 60 μmol), TBD (16.7 mg, 120 μmol), THT (26.5 μL, 0.300 mmol), CuI (57.1 mg, 0.300 mmol), NaH (95 %, 168 mg, 6.60 mmol), **2b** (780 mg, 6.00 mmol), **1** (1.06 g, 6.60 mmol), and dry THF (12 mL). Complete conversion was reached after the reaction mixture had been stirred for 2 h at RT (monitored by TLC: R_f(**2b**) = 0.41 (petroleum ether/ethyl acetate 5:1)), and a workup was carried out. ^{1}H NMR spectroscopic analysis of the crude product was used for determination of the ratio of the regioisomers (**3b**/**4b** 94:6). The crude product was subjected to flash chromatography on silica (50 g, petroleum ether/ethyl acetate 5:1) to yield a mixture of **3b** and **4b** (980 mg, 76 %) as a colorless oil. R_f(**3b**) = 0.10 (petroleum ether/ethyl acetate 5:1); ^{1}H NMR (300 MHz, $CDCl_3$): mixture of branched diastereoisomers in ratio 52:48; δ = 5.77 (ddd, *J* = 17.4, 10.2, 7.7 Hz, 2 H; 2×C*H*=CH$_2$), 5.13–4.95 (m, 4 H; 2×CH=C*H*$_2$), 3.72–3.65 (m, 14 H; 4×OCH_3, 2×*CH*CO_2CH_3), 3.20 (s, 3 H; NCH_3), 3.16 (s, 3 H; NCH_3), 3.08–2.93 (m, 2 H; 2×*CH*CH_3), 1.09 (d, *J* = 6.8 Hz, 3 H; $CHCH_3$), 1.05 ppm (d, *J* = 6.8 Hz, 3 H; $CHCH_3$); ^{13}C NMR (75 MHz, $CDCl_3$): mixture of branched diastereoisomers; δ = 169.3, 169.2, 169.1, 169.0 (4 s; 4×C=O), 140.5, 140.4 (2 d; 2×*C*H=CH$_2$), 115.3, 115.2 (2 t; 2×CH=*C*H$_2$), 61.5 (2 q; 2×$NOCH_3$), 54.1, 53.8, 52.4, 52.3 (2 d, 2 q; 2×*C*HCO_2CH_3, 2×CO_2*C*H$_3$), 38.0, 37.7 (2 d; 2×*C*HCH_3), 32.5 (2 q; 2×N*C*H$_3$), 18.4, 18.1 ppm (2 q; 2×CH*C*H$_3$); elemental analysis calcd (%) for $C_{10}H_{17}NO_4$: C 55.80, H 7.96, N 6.51; found: C 55.46, H 7.92, N 6.61; HPLC (Daicel AD-H column, *n*-hexane/*i*PrOH 99:1, 20 °C, 210 nm): t_r((*R*)-**3b**) = 36/43, t_r((*S*)-**3b**) = 41/47 min, 95 % *ee* for each diastereoisomer.

Methyl (3*R*)-2-{[methoxy(methyl)amino]carbonyl}-3-octylpent-4-enoate (3c): **GP1** was carried out with $[IrCl(cod)]_2$ (129 mg, 0.192 mmol), (*S*,*S*,*aS*)-**L1** (207 mg, 0.384 mmol), TBD (107 mg, 0.770 mmol), THT (169 μL, 1.92 mmol), CuI (366 mg, 1.92 mmol), NaH (95 %, 300 mg, 12.5 mmol), **2c** (2.2 g, 9.6 mmol), **1** (2.01 g, 12.5 mmol), and dry THF (38 mL). Complete conversion was reached after the reaction mixture had been stirred for 18 h at RT (monitored by TLC), and a workup was carried out. The ratio of the regioisomers (**3c**/**4c** 83:17) was determined by ^{1}H NMR spectroscopic analysis of the crude product. The crude product was subjected to flash chromatography on silica (petroleum ether/ethyl acetate 3:1) to yield **3c** and **4c** (2.63 g, 89 %) as a colorless oil. R_f(**3c**) = 0.17 (petroleum ether/ethyl acetate 5:1); ^{1}H NMR (300 MHz, $CDCl_3$): mixture of branched epimers in a ratio of 61:39; δ = 5.70–5.54 (m, 1 H; 2×C*H*=CH$_2$), 5.12–5.01 (m, 2 H; 2×CH=C*H*$_2$), 3.71–3.61 (m, 1 H; 2×*CH*$COOCH_3$), 3.71 (s, 3 H; OCH_3), 3.69 (s, 3 H; OCH_3), 3.69 (s, 3 H; OCH_3), 3.65 (s, 3 H; OCH_3), 3.20 (s, 3 H; NCH_3), 3.15 (s, 3 H; NCH_3), 2.91–2.75 (m, 1 H; 2×CH), 1.36–1.12 (m, 14 H; 2×$CH_{2(n\text{-octyl})}$), 0.91–0.82 ppm (m, 3 H; 2×$CH_{3(n\text{-octyl})}$); ^{13}C NMR (75 MHz, $CDCl_3$): mixture of branched epimers; δ = 169.5, 169.1 (2 s; 2×C=O), 138.9 (d; 2×*C*H=CH$_2$), 117.2 (t; 2×CH=*C*H$_2$), 61.6, 61.6 (2 q; OCH_3), 53.7, 53.1 (2 d; 2×*C*H$COOCH_3$), 52.3, 52.2 (2 q; 2×OCH_3), 44.1 (d; 2×CH), 32.9 (t; $CH_{2(n\text{-octyl})}$), 32.6 (q; 2×NCH_3), 32.5 (t; 2×$CH_{2(n\text{-octyl})}$), 32.0 (t; 2×$CH_{2(n\text{-octyl})}$), 29.7, 29.7 (t; 2×$CH_{2(n\text{-octyl})}$), 29.6, 29.4 (t; 2×$CH_{2(n\text{-octyl})}$), 27.3, 27.2 (t; 2×$CH_{2(n\text{-octyl})}$), 22.8 (t; 2×$CH_{2(n\text{-octyl})}$), 14.2 ppm (q; 2×$CH_{3(n\text{-octyl})}$); elemental analysis calcd (%) for $C_{17}H_{31}NO_4$: C: 65.14, H: 9.97, N: 4.47; found: C 65.29, H 9.89, N 4.49; HPLC (**3c**; Daicel AD-H column, *n*-hexane/*i*PrOH 99:1, 20 °C, 220 nm): t_r((*R*)-**3c**) = 26/28, t_r((*S*)-**3c**) = 27/32 min.

Methyl (3*R*)-3-({[*tert*-butyl(diphenyl)silyl]oxy}methyl)-2-{[methoxy(methyl)amino]carbonyl}pent-4-enoate (3d): **GP1** was carried out with $[IrCl(cod)]_2$ (33.5 mg, 50.0 μmol), (*S*,*S*,*aS*)-**L1** (54.0 mg, 0.100 mmol), TBD (27.8 mg, 0.200 mmol), THT (44 μL, 0.50 mmol), CuI (95 mg, 0.50 mmol), NaH (95 %, 139 mg, 5.50 mmol), **2d** (1.89 g, 4.9 mmol), **1** (935 mg, 5.80 mmol), and dry THF (17 mL). Complete conversion was reached after the reaction mixture had been stirred for 6 h at RT (monitored by TLC: R_f(**2d**) = 0.43 (petroleum ether/ethyl acetate 5:1)) and a workup was carried out. ^{1}H NMR spectroscopic analysis of the crude product was used for determination of the ratio of the regioisomers, (**3d**/**4d** 86:14). The crude product was subjected to flash chromatography on silica (30 g, petroleum ether/ethyl acetate 5:1) to yield a mixture of **3d** and **4d** (1.96 g, 85 %) as a colorless oil. For the branched epimers a ratio of (+)-(2*S*,3*R*)-**3d**/(+)-(2*R*,3*R*)-**3d** 47:53 was determined by ^{1}H NMR spectroscopy. Compounds (+)-(2*S*,3*R*)-**3d**, (+)-(2*R*,3*R*)-**3d**, and **4d** were separated by HPLC (petroleum ether/ethyl acetate 5:1, Latek, 250×21 mm, 5 μ silica, 20 mL min^{-1}, 50 bar), and their absolute and relative configurations were determined by X-ray crystal structure analysis of (2*R*,3*R*)-**3d**.

*Compound (+)-(*2S,3R*)-**3d***: Colorless oil; R_f(**3d**) = 0.08 (petroleum ether/ethyl acetate 5:1); $[\alpha]_D^{20} = +42$ ($c = 0.99$ in $CHCl_3$, 99% *ee* according to HPLC after decarboxylation); ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 7.65$–7.62 (m, 4H; Ar), 7.43–7.35 (m, 6H; Ar), 5.98 (ddd, $J = 17.2$, 10.0, 9.4 Hz, 1H; C*H*=CH$_2$), 5.11 (d, $J = 17.3$ Hz, 1H; CH=C*H*$_2$), 5.08 (d, $J = 10.2$ Hz, 1H; CH=C*H*$_2$), 4.37 (d, $J = 9.2$ Hz, 1H; C*H*CO$_2$CH$_3$), 3.82–3.77 (m, 2H; OC*H*$_2$), 3.72, 3.65 (2s, 6H; 2×OCH$_3$), 3.18 (s; NCH$_3$), 3.10–3.04 (m, 1H; C*H*CH=CH$_2$), 1.06 ppm (s, 9H; C(CH$_3$)$_3$); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 169.5$ (s; C=O), 136.3 (d; *C*H=CH$_2$), 135.7 (d; Ar), 133.6, 133.6 (2s; 2×Ar), 129.8, 129.8, 127.8, (3d; Ar), 118.0 (t, CH=*C*H$_2$), 65.2 (t, OCH$_2$), 61.5, 52.4 (2q, 2×OCH$_3$), 48.3 (d; *C*HCO$_2$CH$_3$), 46.4 (d; *C*HCH=CH$_2$), 32.5 (q; NCH$_3$), 27.0 (q; C(*C*H$_3$)$_3$), 19.5 ppm (s; *C*(CH$_3$)$_3$); HRMS (FAB): *m/z*: calcd for $C_{26}H_{36}NO_5Si$: 470.2363 $[M+H]^+$; found: 470.2334; elemental analysis calcd (%) for $C_{26}H_{35}NO_5Si$: C 66.49, H 7.51, N 2.98; found: C 66.29, H 7.37, N 3.04.

Compound (+)-(2R,3R)-***3d***: Pure (+)-**3d** crystallized as colorless polyhedral crystals; m.p. 63–66 °C; $[\alpha_D^{20} = +30.9$ ($c = 1.02$ in $CHCl_3$, 95.5% *ee* according to HPLC after decarboxylation); ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 7.66$–7.61 (m, 4H; Ar), 7.43–7.34 (m, 6H; Ar), 5.97 (ddd, $J = 17.2$, 10.2, 9.3 Hz, 1H; C*H*=CH$_2$), 5.12 (d, $J = 17.1$ Hz, 1H; CH=C*H*$_2$), 5.09 (d, $J = 10.3$ Hz, 1H; CH=C*H*$_2$), 4.23 (d, $J = 8.4$ Hz, 1H; C*H*CO$_2$CH$_3$), 3.78 (dd, $J = 10.1$, 4.5 Hz, 1H; OC*H*$_a$H$_b$), 3.73 (dd, $J = 10.0$, 5.0 Hz, 1H; OCH$_a$*H*$_b$), 3.67, 3.66 (2s, 6H; 2×OC*H*$_3$), 3.17 (s; NCH$_3$), 3.10 (ddd, $J =$ 13.6, 9.0, 4.7 Hz, 1H; C*H*CH=CH$_2$), 1.05 ppm (s, 9H; C(CH$_3$)$_3$); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 169.3$, 169.2 (2s, 2×C=O), 136.4 (d; *C*H=CH$_2$), 135.8, 135.7 (2d; Ar), 133.7, 133.5, (2s, 2×Ar), 129.8, 129.8, 127.8, (3d; Ar), 117.6 (t; CH=*C*H$_2$), 65.1 (t; OCH$_2$), 61.5, 52.2 (2q; 2×OCH$_3$), 49.3 (d; *C*HCO$_2$CH$_3$), 45.7 (d; *C*HCH=CH$_2$), 32.7 (q; NCH$_3$), 27.0 (q; C(*C*H$_3$)$_3$), 19.5 ppm (s; *C*(CH$_3$)$_3$); HRMS (FAB): *m/z*: calcd for $C_{26}H_{36}NO_5Si$: 470.2363; found: 470.2338 $[M+H]^+$; elemental analysis calcd (%) for $C_{26}H_{35}NO_5Si$: C 66.49, H 7.51, N 2.98; found: C 66.23, H 7.49, N 2.95.

Methyl (4*E*)-2-{[methoxy(methyl)amino]carbonyl}-5-phenylpent-4-enoate (4a): Malonic amide **1** (209 mg, 1.30 mmol) was added to a suspension of NaH (95%, 33 mg, 1.3 mmol) in dry THF (3.5 mL) in a flame-dried Schlenk tube at RT under an argon atmosphere. The mixture was stirred for 10 min to form a clear solution, which was added to a solution of [Pd(C$_3$H$_5$)Cl]$_2$ (7.3 mg, 20 μmol), dppf (dppf = 1,1′-diphenylphosphinoferrocene; 22 mg, 40 μmol), and carbonate **2a** (192 mg, 1.00 mmol) in dry THF (2.5 mL), which had been prepared in a second flame-dried Schlenk tube under an argon atmosphere. The reaction mixture was stirred for 90 min at RT until TLC analysis (R_f(**2a**) = 0.41 (petroleum ether/ethyl acetate 5:1)) indicated complete consumption of the substrate. Diethyl ether (10 mL) and a saturated aqueous solution of NH_4Cl (10 mL) were added, and the phases were separated. The aqueous layer was extracted with diethyl ether (2×20 mL), and the combined organic phases were washed with brine (20 mL), dried over Na_2SO_4, filtered, and concentrated in vacuo. The crude product was purified by flash chromatography on silica (petroleum ether/ethyl acetate 5:1) to yield **4a** (170 mg, 61%) as an analytically pure colorless oil. R_f(**4a**) = 0.06 (petroleum ether/ethyl acetate 5:1); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 7.15$–7.33 (m, 5H; Ph-H), 6.46 (d, $J = 15.8$ Hz, 1H; Ph-C*H*), 6.17 (dt, $J = 15.6$, 7.4 Hz, 1H; Ph-CH=C*H*), 3.84 (d, $J = 7.4$ Hz, 1H; C*H*CO$_2$CH$_3$), 3.70, 3.67 (2s, 6H; 2×OC*H*$_3$), 3.19 (s, 3H; NCH$_3$), 2.86–2.71 ppm (m, 2H, CH$_2$); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 170.0$, 169.7 (2s; 2×C=O), 137.3 (s; Ph-C), 132.7 (d; Ph-*C*H), 128.6, 127.4, 126.4, 126.3 (4d; 3×Ph-C, Ph-CH=*C*H), 61.5, 52.5 (2q; 2×OCH$_3$), 48.7 (d; *C*HCO$_2$CH$_3$), 32.6 (q; NCH$_3$), 32.3 ppm (t; CH$_2$); elemental analysis calcd (%) for $C_{15}H_{19}NO_4$: C 64.97, H 6.91, N 5.05; found: C 64.78, H 6.97, N 5.07; HPLC (Daicel AD-H column, *n*-hexane/*i*PrOH 95:5, 20 °C, 210 nm): t_r(**4a**) = 39/42 min.

Methyl (4*E*)-2-{[methoxy(methyl)amino]carbonyl}hex-4-enoate (4b): Malonic amide **1** (419 mg, 2.60 mmol) was transformed into a solution of the sodium salt as described above in the procedure for preparation of **4a**. This solution was added to a solution of [Pd$_2$(dba)$_3$] (dba = dibenzylidene acetone) (20.7 mg, 20.0 μmol), dppe (dppe = 1,2-bis(diphenyphosphino)ethane) (15.9 mg, 40.0 μmol), and carbonate **2b** (260 mg, 2.00 mmol) in dry THF (2 mL). The reaction mixture was stirred at RT overnight until TLC analysis (R_f(**2b**) = 0.57, (petroleum ether/ethyl acetate 5:1)) indicated complete consumption of the substrate. After workup as described above, the crude product was subjected to flash chromatography on silica (20 g, petroleum ether/ethyl acetate 5:1) to yield a mixture of the regioisomers **3b** and **4b** (**3b**/**4b** 40:60, 371 mg, 86%) as a colorless oil. Separation of the mixture by flash chromatography on silica (20 g, petroleum ether/ethyl acetate 5:1) yielded analytically pure **4b** (110 mg, 26%) as a colorless oil. R_f(**4b**) = 0.10 (petroleum ether/ethyl acetate 5:1); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 5.60$–5.30 (m, 2H; C*H*=C*H*), 3.75–3.67 (m, 1H; CH), 3.70, 3.68 (2s, 6H; 2 OC*H*$_3$), 3.20 (s, 3H; NCH$_3$), 2.60–2.53 (m, 2H; CH$_2$), 1.63 ppm (dd, $J = 6.1$, 1.3 Hz, 3H; CHC*H*$_3$); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 170.2$, 169.9 (2s; 2×C=O), 128.2, 127.2 (2d; *C*H=*C*H), 61.5, 52.4 (2q; 2×OCH$_3$), 48.9 (d; *C*HCO$_2$CH$_3$), 32.6 (q; NCH$_3$), 31.9 (t; C-2), 18.0 ppm (q; CHCH$_3$); HRMS (EI): *m/z*: calcd for $C_{10}H_{17}NO_4$: 215.1158; found: 215.1168 $[M]^+$; elemental analysis calcd (%) for $C_{10}H_{17}NO_4$: C 55.80, H 7.96, N 6.51; found: C 55.58, H 8.00, N 6.62; HPLC(Daicel AD-H column, *n*-hexane/*i*PrOH 99:1, 20 °C, 210 nm): t_r(**4b**) = 58/64 min.

Methyl (4*E*)-2-{[methoxy(methyl)amino]carbonyl}tridec-4-enoate (4c): Malonic amide **1** (97 mg, 0.60 mmol) was transformed into a solution of the sodium salt as described above in the procedure for the preparation of **4a**. The solution was added to a solution of [Pd$_2$(dppf)Cl$_2$]·CH$_2$Cl$_2$ (8.2 mg, 20 μmol) and carbonate **2c** (114 mg, 0.50 mmol) in dry THF (0.75 mL), and the reaction mixture was stirred at RT for 2 h. After workup as described above, the crude product was subjected to flash chromatography on silica (petroleum ether/ethyl acetate 5:1) to yield **4c** (116 mg, 74%) as a colorless, analytically pure oil. R_f(**4c**) = 0.13 (petroleum ether/ethyl acetate 5:1); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 5.56$–5.31 (m, 2H; CH=CH), 3.69, 3.68 (2s, 6H; OCH$_3$), 3.76–3.61 (m, 1H; CH), 3.20 (s, 3H; NCH$_3$), 2.57 (dd, $^3J = 6.3$, 6.3 Hz, 2H; CH$_2$), 1.95 (dt, $^3J = 6.6$, 6.6 Hz, 2H; CH$_{2(n\text{-octyl})}$), 1.37–1.17 (m, 12H; CH$_{2(n\text{-octyl})}$), 0.87 ppm (t, $^3J =$ 7.0 Hz, 3H; CH$_{3(n\text{-octyl})}$); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 170.2$, 169.9 (2s; C=O), 133.9, 125.9 (2d; *C*H=*C*H), 61.5, 52.3 (2q; OCH$_3$), 48.9 (d; CH), 32.6 (q; NCH$_3$), 32.5 (t; CH$_2$), 32.0, 31.9, 29.6, 29.5, 29.4, 29.3, 22.8 (7t; CH$_{2(n\text{-octyl})}$), 14.2 ppm (q; CH$_{3(n\text{-octyl})}$); elemental analysis calcd (%) for $C_{17}H_{31}NO_4$: C 65.14, H 9.97, N 4.47; found: C 65.11, H 9.88, N 4.77; HPLC (Daicel AD-H column, 99:1 *n*-hexane/*i*PrOH, 20 °C, 220 nm): t_r-(**4c**) = 31/32 min.

Methyl (4*E*)-6-{[*tert*-butyl(diphenyl)silyl]oxy}-2-{[methoxy(methyl)amino]carbonyl}hex-4-enoate (4d): This compound was obtained as a side product in the preparation of **3d** (see above). ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 7.69$–7.66 (m, 4H; Ar), 7.43–7.36 (m, 6H; Ar), 5.76–5.65 (m, 2H; C*H*=C*H*), 4.16 (d, $J = 2.5$ Hz, 2H; CH$_2$O), 3.82 (t, $J = 6.6$ Hz, 1H; C*H*CO$_2$CH$_3$), 3.71, 3.68 (2s, 6H; 2×OC*H*$_3$), 3.20 (s, 3H; NCH$_3$), 2.71–2.62 (m, 2H; C*H*$_2$), 1.06 ppm (s, 9H; *t*Bu); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 170.0$, 169.6 (2s, 2×C=O), 135.5 (d; Ar), 133.7 (s; Ar), 131.7 (d; CH=CH), 129.6, 127.7 (2d; 2× C, Ar), 126.5 (d; CH=CH), 64.1 (t; OCH$_2$), 61.4, 52.3 (2q; 2×OCH$_3$), 48.4 (d; *C*HCO$_2$CH$_3$), 32.4 (q; NCH$_3$), 31.4 (t; *C*H$_2$), 26.8 (q; C(*C*H$_3$)$_3$), 19.2 ppm (s; *C*(CH$_3$)$_3$); HRMS (EI): *m/z*: calcd for $C_{26}H_{35}NO_5Si$: 469.2284; found: 469.2272 $[M]^+$; elemental analysis calcd (%) for $C_{26}H_{35}NO_5Si$: C 66.49, H 7.51, N 2.98; found: C 66.21, H 7.51, N 3.12.

(+)-(3*S*)-*N*-methoxy-*N*-methyl-3-phenylpent-4-enamide (5a): A solution of **3a** (containing <2% of **4a**) (1.90 g, 6.88 mmol) and aqueous NaOH (2N, 22 mL) in methanol (65 mL) was stirred for 4 h at RT and was then acidified to pH 1 with aqueous HCl (2N) and extracted with CH_2Cl_2 (3× 50 mL). The combined organic phases were washed with brine (50 mL), dried over Na_2SO_4, filtered and concentrated in vacuo to give a yellowish oil. A small amount of 2,6-di-*tert*-butyl-4-methylphenol (<0.1 mg) was added as radical inhibitor, and the mixture was heated at 210 °C (oil bath temperature). TLC analysis (R_f(carboxylic acid) = 0.00 (petroleum ether/ethyl acetate 3:1)) indicated complete decarboxylation after 20 min. Flash chromatography on silica (30 g, petroleum ether/ethyl acetate 3:1) gave amide **5a** (1.3 g, 87%) as a colorless oil. R_f(**5a**) = 0.19 (petroleum ether/ethyl acetate 3:1); $\alpha_D^{25} = +1.1$ ($c = 0.62$ in MeOH); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 7.27$–7.16 (m, 5H; Ar), 6.08–5.96 (m, 1H; C*H*=CH$_2$), 5.08–5.02 (m, 2H; CH=C*H*$_2$), 4.01–3.94 (m, 1H; CH), 3.57 (s, 3H; NOCH$_3$), 3.11 (s, 3H; NCH$_3$), 2.93–2.76 ppm (m, 2H; CH$_2$); ^{13}C NMR ($CDCl_3$, 75 MHz): $\delta = 172.7$ (s; C=O), 143.4 (s; Ar), 140.9 (d; *C*H=CH$_2$),

128.6, 127.9, 126.6 (3d; Ar), 114.7 (t; CH=*C*H$_2$), 61.4 (q; NOCH$_3$), 45.0 (d; CH), 37.6 (t; CH$_2$), 32.3 ppm (q; NCH$_3$); elemental analysis calcd (%) for $C_{13}H_{17}NO_2$: C 71.21, H 7.81, N 6.39; found: C 71.27, H 7.83, N 6.55.

(+)-(3*S*)-*N*-methoxy-*N*,3-dimethylpent-4-enamide (5b): A mixture of esters **3b** and **4b** (843 mg, 3.92 mmol), obtained by iridium-catalyzed allylic alkylation according to Table 1, entry 4 (**3b**/**4b** 94:6), was saponified as described for ester **3a**. The decarboxylation was conducted by heating at 160 °C for 2 h. Flash chromatography on silica (30 g, petroleum ether/ethyl acetate 5:1) yielded **5b** (517 mg, 84 %) as colorless, analytically pure oil. R_f(**5b**) = 0.13 (petroleum ether/ethyl acetate 5:1); $[\alpha]_D^{20}$ = +1.3 (c = 1.30 in MeOH); ^{1}H NMR (300 MHz, CDCl$_3$): δ = 5.81 (ddd, J = 17.3, 10.4, 6.8 Hz, 1H; C*H*=CH$_2$), 5.03 (ddd, J = 17.1, 1.5, 1.5 Hz, 1H; CH=C*H*$_2$), 4.95 (ddd, J = 10.4, 1.3, 1.3 Hz, 1H; CH=C*H*$_2$), 3.67 (1s, 3H; OCH$_3$), 3.18 (s, 3H; NCH$_3$), 2.81–2.72 (m, 2H; C*H*CH$_3$), 2.49 (dd, J = 15.1, 7.0 Hz, 1H; C*H*$_a$H$_b$CO), 2.36 (dd, J = 15.2, 7.6 Hz, 1H; CH$_a$*H*$_b$CO), 1.06 ppm (d, J = 6.8 Hz, 3H; CHC*H*$_3$); ^{13}C NMR (CDCl$_3$, 75 MHz): δ = 173.5 (s; C=O), 143.4 (d; *C*H=CH$_2$), 113.1 (t; CH=*C*H$_2$), 61.4 (q; OCH$_3$), 38.7 (t; *C*H$_2$CO), 33.9 (d; *C*HCH$_3$), 32.3 (q; NCH$_3$), 19.9 ppm (q; CH*C*H$_3$); HRMS (EI): m/z: calcd for $C_8H_{15}NO_2$: 157.1103, found: 157.1108 $[M]^+$; elemental analysis calcd (%) for $C_8H_{15}NO_2$: C 61.12, H 9.62, N 8.91; found: C 60.86; H 9.54; N 9.17.

(3*S*)-*N*-Methoxy-*N*-methyl-3-octylpent-4-enamide (5c): A mixture of esters **3** and **4c** (2.0 g, 6.4 mmol), obtained from the iridium-catalyzed allylic alkylation according to Table 1, entry 5 (**3c**/**4c** 83:17), was saponified as described for ester **5a**. The decarboxylation was conducted by heating at 210 °C for 20 min. Purification of the brown crude product by flash chromatography on silica (100 g, petroleum ether/ethyl acetate 5:1) yielded amide **5c** (1.4 g 88 %), still contaminated by the corresponding linear regioisomer, as a yellowish oil. R_f(**5c**) = 0.27 (petroleum ether/ethyl acetate 5:1); ^{1}H NMR (300 MHz, CDCl$_3$): δ = 5.72–5.57 (m, 1H; CH, C*H*=CH$_2$), 5.06–4.95 (m, 2H; CH=C*H*$_2$), 3.72–3.65 (m, 3H; OCH$_3$), 3.20–3.16 (m, 3H; NCH$_3$), 2.66–2.25 (m, 3H; CH, CH$_2$), 1.34–1.13 (m, 14H; CH$_{2(n\text{-octyl})}$), 0.87 ppm (t, J = 6.9 Hz, 3H; CH$_{3(n\text{-octyl})}$); ^{13}C NMR (75 MHz, CDCl$_3$): δ = 173.6 (C=O), 142.0 (d; *C*H=CH$_2$), 114.8 (t; CH=*C*H$_2$), 61.4 (q; OCH$_3$), 40.1 (t; CH$_2$), 37.6 (d; CH), 34.8 (q; NCH$_3$), 32.0, 29.8, 29.7, 29.6, 29.4, 27.3, 22.8 (7t; CH$_{2(n\text{-octyl})}$), 14.3 ppm (q; CH$_{3(n\text{-octyl})}$); elemental analysis calcd (%) for $C_{15}H_{29}NO_2$: C 70.54, H 11.45, N 5.48; found: C 70.72, H 11.54, N 5.56.

(+)-(3*S*)-3-({[*tert*-Butyl(diphenyl)silyl]oxy}methyl)-*N*-methoxy-*N*-methylpent-4-enamide (5d): A solution of amides **3d** and **4d** (2.17 g, 4.62 mmol), obtained by iridium-catalyzed allylic alkylation according to Table 1, entry 7 (**3d**/**4d** 85:15), in THF (10 mL) was added to an aqueous solution of LiOH (1 M, 10 mL) and the resulting mixture was stirred at RT for 18 h. The solution was acidified to pH 2 with aqueous 2 N HCl, and the aqueous phase was extracted with CH_2Cl_2 (3 × 50 mL). The combined organic phases were dried over Na_2SO_4, filtered, and concentrated in vacuo. A small amount (< 0.1 mg) of 2,6-di-*tert*-butyl-4-methylphenol was added to the crude product as a radical inhibitor and then the mixture was heated to 200 °C (oil bath temperature) for 30 min until TLC analysis indicated complete decarboxylation. Purification of the dark crude product by flash chromatography on silica (50 g, petroleum ether/ethyl acetate 5:1) yielded (+)-(3*S*)-**5d** (1.34 g, 70 %) as a slightly yellow, analytically pure oil. R_f(**5d**) = 0.18 (petroleum ether/ethyl acetate 5:1); $[\alpha]_D^{20}$ = +14.2 (c = 1.02 in CHCl$_3$, 97.5 % *ee* according to HPLC); ^{1}H NMR (500 MHz, CDCl$_3$): δ = 7.68–7.65 (m, 4H; Ar), 7.44–7.36 (m, 6H; Ar), 5.81 (ddd, J = 17.4, 10.0, 7.6 Hz, 1H; C*H*=CH$_2$), 5.09 (d, J = 17.1 Hz, 1H; CH=C*H*$_2$), 5.05 (d, J = 10.3 Hz, 1H; CH=C*H*$_2$), 3.71 (dd, J = 9.8, 4.9 Hz; 1H; OC*H*$_a$H$_b$), 3.67 (s, 3H; OCH$_3$), 3.62 (dd, J = 9.8, 6.4 Hz, 1H; OCH$_a$*H*$_b$), 3.17 (s, 3H; NCH$_3$), 2.94–2.88 (m, 1H; C*H*CH=CH$_2$), 2.75 (dd, J = 15.4, 5.1 Hz, 1H; C*H*$_2$C=O), 2.54 (dd, J = 14.2, 8.3 Hz, 1H; C*H*$_2$C=O), 1.06 ppm (s, 9H; *t*Bu-H), ^{13}C NMR (CDCl$_3$, 125 MHz): δ = 173.5 (s; C=O), 138.9 (d; *C*H=CH$_2$), 135.8 (d; Ar), 133.8 (s; Ar), 129.7, 127.8 (2d; Ar), 116.0 (t; CH=*C*H$_2$), 66.8 (t; OCH$_2$), 61.3 (q; OCH$_3$), 42.1 (d; *C*HCH=CH$_2$), 33.5 (t; *C*H$_2$C=O), 32.2 (q; NCH$_3$), 27.0 (q; C(*C*H$_3$)$_3$), 19.5 ppm (s; *C*(CH$_3$)$_3$); HRMS (FAB): m/z: calcd for $C_{24}H_{34}NO_3Si$: 412.2308; found: 412.2320 $[M+H^+]$; elemental analysis calcd (%) for $C_{24}H_{33}NO_3Si$: C 70.03, H 8.08, N 3.40; found: C 69.94, H 8.10, N 3.44; HPLC (Daicel AD-H column, *n*-hexane/*i*PrOH 99.5:0.5, 20 °C, 230 nm): t_r((*S*)-**5d**) = 33.5, t_r((*R*)-**5d**) = 37.5 min.

(5*S*)-5-Octylhepta-1,6-dien-3-one (6d): A solution of amide **5c** (1.2 g, 4.7 mmol), contaminated with the linear regioisomer, in dry THF (30 mL) was cooled to −78 °C and then treated dropwise with a 1 M solution of bromo(vinyl)magnesium in THF (12.2 mL). The reaction mixture was stirred for 1 h and then allowed to warm to 0 °C. After further 2 h, TLC analysis indicated complete consumption of **5c**. The mixture was added dropwise to a cold (0 °C) saturated aqueous solution of $NaHSO_4$ (50 mL). The mixture was extracted with diethyl ether (3 × 50 mL), and the combined organic phases were washed with brine (100 mL), dried over Na_2SO_4, filtered and concentrated in vacuo to give a yellow oil. This was subjected to flash chromatography on silica (petroleum ether/ethyl acetate 15:1) to yield diene **6d** (0.86 g, 82 %), contaminated with the linear regioisomer, as a yellowish oil. R_f(**6d**) = 0.64 (petroleum ether/ethyl acetate 5:1); ^{1}H NMR (300 MHz, CDCl$_3$): δ = 6.35 (dd, J = 16.6, 10.3 Hz, 1H; (CO)C*H*=CH$_2$), 6.19 (dd, J = 17.6, 1.2 Hz, 1H; (CO)CH=C*H*$_2$), 5.80 (dd, J = 10.4, 1.4 Hz, 1H; (CO)CH=C*H*$_2$), 5.67–5.34 (m, 1H; C*H*=CH$_2$), 5.00–4.94 (m, 2H; CH=C*H*$_2$), 2.67–2.54 (m, 3H; CH, CH$_2$), 1.42–1.17 (m, 14H; CH$_{2(n\text{-octyl})}$), 0.87 ppm (t, ^3J = 6.5 Hz, 3H; CH$_{3(n\text{-octyl})}$); ^{13}C NMR (75 MHz, CDCl$_3$): δ = 200.1 (s; C=O), 141.6 (d; C*H*=CH$_2$), 137.1 (d; (CO)C*H*=CH$_2$), 128.1 (t; (CO)CH=C*H*$_2$), 114.8 (t; CH=C*H*$_2$), 45.2 (t; CH$_2$), 39.8 (d; CH), 34.8, 32.0, 29.7, 29.7, 29.4, 27.2, 22.8 (7t; CH$_{2(n\text{-octyl})}$), 14.2 ppm (q; CH$_{3(n\text{-octyl})}$); elemental analysis calcd (%) for $C_{15}H_{26}O$: C 81.02, H 11.79; found: C 80.81, H 11.64.

(5*S*)-2-Methyl-5-octylhepta-1,6-dien-3-one (6e): A solution of a Grignard reagent was prepared from activated magnesium turnings (56.0 mg, 2.34 mmol), 2-bromopropene (254 mg, 2.23 mmol), and THF (3.5 mL). This was cannulated into a cooled (−78 °C) solution of **5c** (200 mg, 0.780 mmol), contaminated with the linear regioisomer, in THF (35 mL). The mixture was stirred at −78 °C for 1 h and at 0 °C for 2 h. TLC analysis indicated complete consumption of **5c**. A solution of saturated aqueous $NaHSO_4$ (10 mL) was added, and the mixture was extracted with diethyl ether (3 × 50 mL). The combined organic phases were dried over Na_2SO_4, filtered, and concentrated in vacuo. The residue was subjected to flash chromatography on silica (40 g, petroleum ether/ethyl acetate 10:1) to yield the dienone **6e**, contaminated with the linear regioisomer, as a colorless oil (160 mg, 87 %). R_f(**6e**) = 0.61 (petroleum ether/ethyl acetate 5:1); $[\alpha]_D^{20}$ = +44.6 (c = 0.73 in CHCl$_3$); ^{1}H NMR (300 MHz, CDCl$_3$): δ = 6.01–5.89 (m, 1H; C=CH$_2$), 5.78–5.73 (m, 1H; C=CH$_2$), 5.68–5.54 (m, 1H; C*H*=CH$_2$), 5.61 (ddd, J = 17.7, 8.0, 1.2 Hz, 1H; C*H*=CH$_2$), 5.00–4.91 (m, 2H; CH=C*H*$_2$), 2.76–2.51 (m, 3H; CH$_2$, CH), 1.87–1.83 (m, 3H; CH$_3$), 1.39–1.16 (m, 14H; 7 × CH$_{2(n\text{-octyl})}$), 0.87 ppm (t, J = 6.0 Hz, 3H; CH$_{3(n\text{-octyl})}$); ^{13}C NMR (75 MHz, CDCl$_3$): δ = 201.6 (s; C=O), 145.2 (s; C=CH$_2$), 141.9 (d; C*H*=CH$_2$), 124.6 (t; C=CH$_2$), 114.7 (t; CH=C*H*$_2$), 43.0 (t; CH$_2$), 40.3 (d; CH), 34.8, 32.0, 29.7, 29.6, 29.4, 27.2, 22.8 (7t; CH$_{2(n\text{-octyl})}$), 17.8 (q; CH$_3$),14.3 ppm (q; CH$_{3(n\text{-octyl})}$); HRMS (EI): m/z: calcd for $C_{16}H_{28}O$: 236.2140; found: 236.2137 $[M]^+$.

(+)-(5*S*)-5-({[*tert*-Butyl(diphenyl)silyl]oxy}methyl)-2-methylhepta-1,6-dien-3-one (6f): A solution of a Grignard reagent was prepared from activated magnesium turnings (780 mg, 32.0 mmol), 2-bromopropene (3.9 g, 32 mmol) and THF (20 mL). This was transferred by cannula into a cooled (−78 °C) solution of pure (+)-**5d** (5.08 g, 12.4 mmol) in THF (35 mL). After the reaction mixture had been stirred for 1 h, the mixture was allowed to warm to 0 °C and was stirred for another 2 h; TLC analysis (R_f(**5d**) = 0.18 (petroleum ether/ethyl acetate 5:1)) indicated complete consumption of the starting material. An aqueous solution of $NaHSO_4$ (10 %, 100 mL) was added. The resultant mixture was extracted with diethyl ether (3 × 100 mL), and the combined organic phases were dried over Na_2SO_4, filtered, and concentrated in vacuo. The crude product was purified by flash chromatography on silica (100 g, petroleum ether/ethyl acetate 5:1) to yield (+)-(**6d**) as a colorless oil (4.58 g, 94 %). R_f(**6f**) = 0.59 (petroleum ether/ethyl acetate 5:1); $[\alpha]_D^{20}$ = +12.3 (c = 0.73 in CHCl$_3$); ^{1}H NMR (300 MHz, CDCl$_3$): δ = 7.67–7.62 (m, 4H; Ar), 7.45–7.34 (m, 6H; Ar), 5.95 (s, 1H; CCH$_3$=C*H*$_2$), 5.81–5.68 (m, 2H; C*H*=CH$_2$, CCH$_3$=C*H*$_2$), 5.08–5.02 (m, 2H; CH=C*H*$_2$), 3.67 (dd, J = 9.9, 5.2 Hz, 1H; OC*H*$_a$H$_b$), 3.57 (dd, J = 9.9, 6.4 Hz, 1H; OCH$_a$*H*$_b$), 3.05 (dd, J = 15.7, 5.4 Hz, 1H; CH$_2$C=O), 2.95–2.84 (m, 1H; C*H*CH=CH$_2$), 2.69 (dd, J =

15.7, 8.0 Hz, 1H; $CH_2C{=}O$), 1.85 (s, 3H; CH_3), 1.05 ppm (s, 9H; *t*Bu); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 201.2$ (s; C=O), 144.9 (s; $CCH_3{=}CH_2$), 138.8 (d; $CH{=}CH_2$), 135.7 (d; Ar), 133.7 (s; Ar), 129.8, 127.8 (2d; Ar), 124.7 (t; $CCH_3{=}CH_2$), 116.0 (t; $CH{=}CH_2$), 66.6 (t; OCH_2), 42.3 (d; $CHCH{=}CH_2$), 38.9 (t; $CH_2C{=}O$), 27.0 (q; $C(CH_3)_3$), 19.4 (s; $C(CH_3)_3$), 17.8 ppm (q; CH_3); HRMS (FAB): *m*/*z*: calcd for $C_{25}H_{33}O_2Si$: 393.2250; found: 393.2229 [M+H$^+$]; elemental analysis calcd (%) for $C_{25}H_{32}O_2Si$: C 76.48, H 8.22; found: C 76.37, H 8.33.

(−)-(4*S*)-4-Phenylcyclopent-2-en-1-one (7a): A solution of (+)-**5a** (88 mg, 0.40 mmol) in dry THF (1 mL) was cooled to −78 °C. Then, a solution of bromo(vinyl)magnesium in THF (1.2 mL, 1 M) was added slowly. After the reaction mixture had been stirred for 1 h, it was allowed to warm to 0 °C. After 2 h, TLC analysis (R_f(**5a**) = 0.15 (petroleum ether/ethyl acetate 3:1)) indicated complete consumption of **5a**. The mixture was added dropwise to an aqueous solution of $NaHSO_4$ (10 mL, 5%) at 0 °C. The mixture was extracted with diethyl ether (3 × 15 mL), and the combined organic phases were washed with brine (30 mL), dried over Na_2SO_4, filtered, and concentrated in vacuo to give a colorless oil as the crude product (**6a**). This was treated with a solution of Grubbs II catalyst (8.0 mg, 10 μmol) in CH_2Cl_2 (3 mL) and the resultant mixture was stirred and heated at reflux for 2 h under an argon atmosphere. The solvent was removed in vacuo to give a dark-brown residue that was subjected to flash chromatography on silica (15 g, R_f(**6a**) = 0.26, petroleum ether/ethyl acetate 10:1) to yield **7a** (48 mg, 76%) as slightly yellow oil. R_f(**7a**) = 0.07 (petroleum ether/ethyl acetate 10:1); $[\alpha]_D^{24} = -284$ ($c = 0.51$ in $CHCl_3$, 97% *ee* according to HPLC); ^1H NMR (300 MHz, $CDCl_3$): $\delta = 7.67$ (dd, $J = 5.6$, 2.6 Hz, 1H; (C=O)CH=C*H*), 7.36–7.13 (m, 5H; Ar), 6.32 (dd, $J = 5.6$, $J = 2.1$ Hz, 1H; (C=O)C*H*=CH), 4.19–4.15 (m, 1H; CH), 2.90 (dd, $J = 18.9$, 6.9 Hz, 1H; CH_{2b}), 2.32 ppm (dd, $J = 18.9$, 2.5 Hz, 1H; CH_{2a}), ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 210.0$ (s; C=O), 166.7 (d; CH=), 141.6 (s; Ar), 134.2 (d; CH=), 129.1, 127.4, 127.3 (3d; Ar), 46.9 (d; CH), 44.1 ppm (t; CH_2); HRMS (EI): *m*/*z*: calcd for $C_{11}H_{10}O$: 158.0732; found: 158.0746 [M^+]; HPLC (Daicel AD-H column, *n*-hexane/*i*PrOH 99.7:0.3, 25 °C, 210 nm): t_r((+)-**7a**) = 108.4 min, t_r((−)-**7a**) = 118.1 min.

(−)-(4*S*)-2,4-Diphenylcyclopent-2-en-1-one (7b): A solution of bromo(1-phenylvinyl)magnesium in THF (2 M, 1.43 mL) was added dropwise to a cooled (−78 °C) solution of amide (+)-**5a** (250 mg, 1.14 mmol) in dry THF (3 mL). After the reaction mixture had been stirred for 1 h, it was allowed to warm to 0 °C. After a further 2 h, TLC analysis (R_f(**6b**) = 0.57, petroleum ether/ethyl acetate 5:1) indicated complete consumption of **5a**. The reaction mixture was added dropwise to a cold (0 °C) saturated aqueous solution of $NaHSO_4$ (50 mL). The resultant mixture was extracted with diethyl ether (3 × 50 mL), and the combined organic phases were washed with brine (100 mL), dried over Na_2SO_4, filtered, and concentrated in vacuo to give **6b** as a yellow oil. This was treated with a solution of Grubbs II catalyst (21 mg, 29 μmol) in CH_2Cl_2 (15 mL) and the resulting solution was vigorously stirred and heated at reflux for 2 h under an argon atmosphere. The mixture was then stirred overnight at RT until TLC analysis indicated complete consumption of the starting material. The solvent was removed in vacuo to give a dark-brown residue, which was subjected to flash chromatography on silica (petroleum ether/ethyl acetate 5:1) to yield cylopentenone **7b** (175 mg, 63% over 2 steps) as a white powder. R_f(**7b**) = 0.43 (petroleum ether/ethyl acetate 5:1); m.p. 63–64 °C; $[\alpha]^D24 = -94$ ($c = 0.50$ in $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): $\delta =$ 7.83–7.74 (m, 3H; Ar, C=CH), 7.45–7.18 (m, 8H; Ar), 4.18 (ddd, $J = 7.0$, 5.4, 2.6 Hz, 1H; PhC*H*), 3.14 (dd, $J = 19.0$, 7.1 Hz, 1H; CH_{2b}), 2.58 ppm (dd, $J = 19.0$, 2.6 Hz, 1H; CH_{2a}); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 207.2$ (s; C=O), 160.7 (d; C=CH), 143.0, 142.1, 131.3, 129.2, 128.9, 128.7, 127.4, 127.4 (8d; Ar, *C*=*C*H), 45.8 (t; CH_2), 43.9 ppm (d; CH); elemental analysis calcd (%) for $C_{17}H_{14}O$: C 87.15, H 6.02; found: C 86.96, H 6.13; HPLC (Daicel AD-H column, *n*-hexane/*i*PrOH 95:5, 20 °C, 254 nm): t_r((+)-**7b**) = 20.7, t_r((−)-**7b**) = 26.9 min].

(−)-(4*S*)-2,4-Dimethylcyclopent-2-en-1-one (7c): A Grignard reagent was prepared from magnesium (194 mg, 8.00 mmol), 2-bromopropene (968 mg, 8.00 mmol), and Et_2O (8 mL). The solution was transferred by cannula into a cooled (−78 °C) solution of (+)-**5b** (393 mg, 2.50 mmol) in Et_2O (8 mL). After the reaction mixture had been stirred at −78 °C for 1 h and at 0 °C for 2 h, TLC analysis (R_f(**6c**) = 0.60 (petroleum ether/ethyl acetate 5:1)) indicated complete consumption of the starting material. The mixture was added dropwise to an aqueous solution of $NaHSO_4$ (10%, 50 mL), which was kept at 0 °C to avoid possible side reactions.[30] The mixture was extracted with diethyl ether (3 × 20 mL), and the combined organic phases were dried over Na_2SO_4, filtered, and concentrated in vacuo to give crude **6c**, a colorless, volatile liquid. This was dissolved in CH_2Cl_2 (15 mL), Grubbs II catalyst (42 mg, 50 μmol) was added, and the vigorously stirred mixture was heated at reflux for 2 h under an argon atmosphere, until TLC analysis indicated complete consumption of the starting material. The reaction flask was connected by a wide glass tube to a second flask. The reaction mixture was cooled to −40 °C, the system evacuated and the solvent was removed, over a period of ca. 3 h, by cooling the second flask to −196 °C. The resulting solvent-free crude product was subjected to the same procedure by vaporization at RT and condensation at −196 °C to remove the catalyst. Ketone (−)-**7c** (144 mg, 52%) was obtained as a colorless, highly volatile liquid with a characteristic odor. The analytical data agreed with the data for the racemic compound published by Ahlbrecht and Daacke.[31] R_f(**7c**) = 0.38, (petroleum ether/ethyl acetate 5:1); $[\alpha]_D^{20} = -164$ ($c = 0.82$ in MeOH, 95.5% *ee* according to HPLC); ^1H NMR (300 MHz, $CDCl_3$): $\delta = 7.19$ (dd, $J = 2.2$, 1.0 Hz, 1H; C=CH), 2.92–2.79 (m, 1H; CH), 2.61 (dd, $J = 18.8$, 6.3 Hz, 1H; CH_2), 1.94 (dd, $J = 18.8$, 1.9 Hz, 1H; CH_2), 1.75 (dd, $J = 1.7$, 1.5 Hz, 3H; CH_3), 1.15 ppm (d, $J = 7.1$ Hz, 3H; CH_3); ^{13}C NMR ($CDCl_3$, 75 MHz): $\delta = 210.3$ (s; C=O), 163.7 (d; C=CH), 141.0 (s; *C*=*C*H), 43.1 (t; CH_2), 33.4 (d; CH), 20.4, 10.1 ppm (2q; 2 × CH_3); HRMS (EI): *m*/*z*: calcd for $C_7H_{10}O$: 110.0732; found: 110.0723 [M]$^+$; HPLC (Daicel AD-H column, *n*-hexane/*i*PrOH 99:1, 7 °C, 220 nm): t_r((−)-(*S*)-**7c**) = 16.5, t_r((+)-(*R*)-**7c**) = 17.6 min.

(−)-(4*S*)-4-Octylcyclopent-2-en-1-one (7d): Diene **6d** (800 mg, 3.60 mmol), contaminated with the linear regioisomer, was dissolved in dry CH_2Cl_2 (100 mL), and Grubbs II catalyst (90 μmol, 76 mg) was added. Under an argon atmosphere, the stirred solution was heated at reflux for 2 h (monitored by TLC). The solvent was removed in vacuo to give a dark-brown residue, which was subjected to flash chromatography on silica (5:1 petroleum ether/ethyl acetate) to yield enone **7d** (0.49 g, 70%) as slightly brown oil. Side products formed from the linear regioisomer were separated off in this step, but they were not isolated. R_f-(**7d**) = 0.21 (petroleum ether/ethyl acetate 5:1); $[\alpha]_D^{24} = -129$ ($c = 0.50$ in $CHCl_3$, 96% *ee* according to HPLC); ^1H NMR (300 MHz, $CDCl_3$): $\delta =$ 7.63 (dd $J = 5.6$, 2.4 Hz, 1H; (C=O)CH=C*H*), 6.13 (dd, $J = 5.7$, 2.0 Hz, 1H; (C=O)C*H*=CH), 2.96–2.86 (m, 1H; =C−CH), 2.52 (dd, $J = 18.8$, 6.3 Hz, 1H; CH_{2b}), 1.99 (dd, $J = 18.8$, 2.1 Hz, 1H; CH_{2a}), 1.68–1.45 (m, 1H; $CH_{2(n\text{-octyl})}$), 1.44–1.19 (m, 13H; $CH_{2(n\text{-octyl})}$), 0.87 ppm (t, $J = 6.5$ Hz, 3H; CH_3); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 210.2$ (s; C=O), 168.8, 137.7 (2d; CH=CH) 41.6 (d; CH), 41.2 (t; CH_2), 34.9, 31.2, 29.7, 29.6, 29.4, 27.8 22.8 (7t; $CH_{2(n\text{-octyl})}$), 14.2 ppm (q; CH_3); HRMS (EI): *m*/*z*: calcd for $C_{13}H_{22}O$: 194.1671; found: 194.1657 [M^+]; HPLC (Daicel AD-H column, *n*-hexane/*i*PrOH 99.8:0.2, 7 °C, 220 nm): t_r((+)-**7d**) = 36.3, t_r((−)-**7d**) = 38.9 min.

(−)-(4*S*)-2-Methyl-4-octylcyclopent-2-en-1-on (7e): Under an argon atmosphere, a stirred solution of dienone **6e** (120 mg, 0.510 mmol), contaminated with the linear regioisomer, and Grubbs II catalyst (11.1 mg, 10.0 μmol) in CH_2Cl_2 (15 mL) was heated at reflux for 3.5 h. The solvent was removed in vacuo to give a dark-brown residue, which was subjected to flash chromatography on silica (20 g, petroleum ether/ethyl acetate 5:1) to yield 69 mg (65%) of cyclopentenone **7e** as a slightly yellow oil; the linear regioisomer was separated off in this step but it was not isolated. R_f(**7e**) = 0.53 (petroleum ether/ethyl acetate 5:1); $[\alpha]_D^{20} = -37.2$ ($c =$ 0.54 in $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$): $\delta = 7.25$–7.22 (m, 1H; C=CH), 2.78–2.71 (m, 1H; =C−CH), 2.55 (dd, $J = 18.5$, 6.5 Hz, 1H; CH_{2a}), 2.00 (dd, $J = 18.5$, 2.0 Hz, 1H; CH_{2b}), 1.76–1.74 (m, 3H; CH_3), 1.54–1.20 (m, 14H; $CH_{2(n\text{-octyl})}$), 0.88 ppm (t, $J = 6.4$ Hz, 3H; $CH_{3(n\text{-octyl})}$); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 210.0$ (s; C=O), 162.4 (d; C=CH), 141.3 (s; *C*=*C*H), 41.5 (d; CH), 39.0 (t; CH_2), 35.3, 32.0, 29.8, 29.6, 29.4, 27.8, 22.8 (7t; $CH_{2(n\text{-octyl})}$), 14.2 (q; $CH_{3(n\text{-octyl})}$), 10.2 ppm (q; CH_3); HRMS (EI): *m*/*z*: calcd for $C_{14}H_{24}O$: 208.1824; found: 208.1819 [M]$^+$.

(−)-(4*S*)-4-({[*tert*-Butyl(diphenyl)silyl]oxy}methyl)-2-methylcyclopent-2-en-1-one (7f): A vigorously stirred solution of (+)-**6f** (4.18 g,

10.60 mmol) and Grubbs II catalyst (90.0 mg, 106 μmol) in CH_2Cl_2 (50 mL) was heated at reflux for 16 h under an argon atmosphere (monitored by TLC: R_f(**6f**) = 0.59 (petroleum ether/ethyl acetate 5:1)). The solvent was removed in vacuo to give a dark-brown residue, which was subjected to flash chromatography on silica (200 g, petroleum ether/ethyl acetate 5:1) to yield **7f** as slightly yellow oil. The product was dissolved in hot methanol and water was added until saturation. Upon cooling of the solution to 5 °C, (−)-**7f** was obtained as colorless polyhedral crystals (3.29 g, 85 %). R_f(**7f**) = 0.37 (petroleum ether/ethyl acetate 5:1); m.p. 52–54 °C; $[\alpha]_D^{20} = -106$ ($c = 1.01$ in $CHCl_3$, 97.5 % *ee* according to HPLC); ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 7.65$–7.60 (m, 4H; Ar), 7.47–7.36 (m, 6H; Ar), (m, 1H; CH=), 3.71 (dd, $J = 9.8$, 5.9 Hz, 1H; OCH_aH_b), 3.66 (dd, $J = 9.8$, 6.4 Hz, 1H; OCH_aH_b), 3.00 (br m, 1H; *CH*CH=), 2.47 (dd, $J = 18.6$, 6.4 Hz, 1H; $CH_2C{=}O$), 2.20 (dd, $J = 19.1$, 1.9 Hz, 1H; $CH_2C{=}O$), 1.78 (s, 3H; CH_3), 1.04 ppm (s, 9H; *t*Bu-H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 209.5$ (s; C=O), 159.3 (d; CH=), 142.8 (s; CH=*C*), 135.7, 135.7 (2d; Ar), 133.5, 133.4 (2s; Ar), 129.9, 129.9, 127.9 (3d; Ar), 66.0 (t; OCH_2), 41.6 (d; *C*HCH=), 37.9 (t; $CH_2C{=}O$), 26.9 (q; $C(CH_3)_3$), 19.4 (s; *C*-$(CH_3)_3$), 10.3 ppm (q; CH_3); HRMS (FAB): *m*/*z*: calcd for $C_{23}H_{29}O_2Si$: 365.1937; found: 365.1943 [*M*+H$^+$]; elemental analysis calcd (%) for $C_{23}H_{28}O_2Si$: C 75.78, H 7.74; found: C 75.52, H 7.73; HPLC (Daicel OD-H column, *n*-hexane/*i*PrOH 90:10, 20 °C, 220 nm): t_r((−)-**7f**) = 10.5, t_r((+)-**7f**) = 14.0 min.

(−)-(12*R*)-Methyl 7-hydroxy-9-oxoprost-10-en-1-oate (8): A solution of iPr_2NH (0.24 mL, 1.7 mmol) in dry THF (5 mL) was treated with *n*BuLi (0.88 mL, 1.6 M in hexane). The resulting solution of LDA was cooled to −78 °C, then enone **7d** (248 mg, 1.27 mmol) was added. The mixture was stirred for 10 min at −78 °C, and then freshly prepared methyl 6-formylhexanoate (269 mg, 1.70 mmol) was added dropwise. After 2 h at −78 °C, TLC analysis indicated complete conversion, and the solution was poured into a cold (0 °C), vigorously stirred mixture of diethyl ether (50 mL) and saturated aqueous NH_4Cl (25 mL). The organic layer was separated, and the aqueous layer was extracted with diethyl ether (3× 50 mL). The combined extracts were dried over $MgSO_4$, filtered and concentrated in vacuo. The crude product was purified by flash chromatography on silica (petroleum ether/ethyl acetate 5:1) to yield alcohol **8** (265 mg, 58 %) as a colorless oil. R_f(**8**) = 0.24 (petroleum ether/ethyl acetate 5:1); $[\alpha]_D^{24} = -81$ ($c = 0.85$ in $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 7.68$ (dd, $J = 5.4$, 2.4 Hz, 1H; 11-H), 6.13 (dd, $J = 5.9$, 2.0 Hz, 1H; 10-H), 3.80 (s, 1H; OH), 3.68–3.65 (m, 1H; 7-H), 3.66 (s, 3H; OCH_3), 2.67–2.61 (m, 1H; 12-H), 2.31 (t, $J = 7.4$ Hz, 2H; 2-H), 2.00 (dd, $J = 8.4$, 2.0 Hz, 1H; 8-H), 1.68–1.21 (m, 22H; 3-H, 4-H, 5-H, 6-H, 13-H, 14-H, 15-H, 16-H, 17-H, 18-H, 19-H), 0.88 ppm (t, $J = 6.4$ Hz, 3H; 20-H); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 213.0$ (s; C-9), 174.3 (s; C-1), 168.7 (d; C-11), 133.0 (d; C-10), 72.3 (d; C-7), 56.2 (d; C-8), 51.6 (q; C-1′), 45.1 (d; C-12), 35.5, 34.1, 34.1, 31.2, 29.9, 29.6, 29.4, 29.2, 27.1, 25.3, 25.1, 22.8 (12t; C-2, C-3, C-4, C-5, C-6, C-13, C-14, C-15, C-16, C-17, C-18, C-19), 14.2 ppm (q; C-20); elemental analysis calcd (%) for $C_{21}H_{36}O_4$: C 71.55, H 10.31; found: C 71.62, H 10.31.

(−)-(12*R*)-Methyl 7-[(methylsulfonyl)oxy]-9-oxoprost-10-en-1-oate (9): A solution of alcohol **8** (120 mg, 0.340 mmol) and dry Et_3N (0.47 mL, 3.4 mmol) in dry CH_2Cl_2 (3 mL) was cooled to 0 °C and freshly distilled MsCl (0.20 mL, 2.5 mmol) was added. The mixture was allowed to warm to RT and was stirred overnight (monitored by TLC). It was then poured into a stirred mixture of ethyl acetate (10 mL) and saturated aqueous $NaHCO_3$ (5 mL). The mixture was extracted with diethyl ether (3× 20 mL), and the organic layer was dried over $MgSO_4$ and concentrated in vacuo. The residue was subjected to flash chromatography on silica (30 g, petroleum ether/ethyl acetate 5:1) to yield mesylate **9** (120 mg, 82 %) as a yellowish oil. R_f(**9**) = 0.12, (petroleum ether/ethyl acetate 5:1); $[\alpha]_D^{24} = -53$ ($c = 0.8$ in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 7.68$ (dd, $J = 5.8$, 2.4 Hz, 1H; 11-H), 6.11 (dd, $J = 5.8$, 1.7 Hz, 1H; 10-H), 5.04–4.95 (m, 1H; 7-H), 3.66 (s, 3H; OCH_3), 3.04–2.99 (m, 1H; 8-H), 3.00 (s, 3H; SCH_3), 2.57–2.52 (m, 1H; 12-H), 2.30 (t, $J = 7.4$ Hz, 2H; 2-H), 1.85–1.16 (m, 22H; 3-H, 4-H, 5-H, 6-H, 13-H, 14-H, 15-H, 16-H, 17-H, 18-H, 19-H), 0.88 ppm (t, $J = 6.8$ Hz, 3H; 20-H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 209.4$ (s; C-9), 173.1 (s; C-1), 168.4 (d; C-11), 133.4 (d; C-10), 82.4 (d; C-7), 54.7 (d; C-12), 51.7 (d; C−OCH_3), 44.2 (d; C-8), 38.6 (q; C−SCH_3), 34.5 (1t; C-2), 34.0, 32.0, 31.2, 29.8, 29.6, 29.4, 28.8, 27.4, 25.7, 24.8, 22.8 (11t; C-3, C-4, C-5, C-6, C-13, C-14, C-15, C-16, C-17, C-18, C-19), 14.2 ppm (q; C-20). HRMS (FAB): *m*/*z*: calcd for $C_{22}H_{39}O_6S$: 431.2467; found: 431.2482 [*M*+H]$^+$.

(−)-(12*R*)-*TEI-9826* (10): A suspension of the mesylate **9** (60 mg, 0.14 mmol) and neutral alumina (150 mg) in dry CH_2Cl_2 (5 mL) was stirred at RT; additional portions of alumina, 130, 90, and 50 mg, were added after 2, 4, and 6 h, respectively. After 18 h, the reaction mixture was filtered through a pad of Celite, which was washed with ethyl acetate. The filtrate was concentrated in vacuo, and the residue was subjected to flash chromatography on silica (petroleum ether/ethyl acetate 5:1) to yield *TEI-9826* (**10**) (44 mg, 94 %) as a yellowish oil. R_f(**10**) = 0.35 (petroleum ether/ethyl acetate 5:1); $[\alpha]_D^{24} = -121$ ($c = 0.58$ in $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 7.53$ (dd, $J = 6.0$, 2.0 Hz, 1H; 11-H), 6.51 (t, $J = 7.8$ Hz, 1H; 7-H), 6.32 (dd, $J = 6.0$, 2.0 Hz, 1H; 10-H), 3.66 (s, 3H; OCH_3), 3.48–3.43 (m, 1H; 12-H), 2.32–2.18 (m, 4H; 2-H, 6-H), 1.85–1.75 (m, 1H; CH_2), 1.68–1.58 (m, 2H; CH_2), 1.55–1.45 (m, 3H; CH_2), 1.42–1.34 (m, 2H; CH_2), 1.33–1.18 (m, 12H; CH_2), 0.87 ppm (t, $J = 7.1$ Hz, 3H; 20-H); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 197.1$, 174.2 (2s; C-1, C-9), 162.1 (d; C-11), 138.3 (s; C-8), 135.3 (d; C-7), 134.9 (d; C-10), 51.6 (q; OCH_3), 43.5 (d; C-12), 34.0, 32.6, 31.2, 29.9, 29.6, 29.4, 29.1, 29.0, 28.5, 26.0, 24.9, 22.8 (12t; C-2, C-3, C-4, C-5, C-6, C-13, C-14, C-15, C-16, C-17, C-18, C-19), 14.2 ppm (q; C-20); elemental analysis calcd (%) for $C_{21}H_{34}O_3$: C 75.41, H 10.25; found: C 75.07, H 10.22; HPLC (Daicel AD-H column, 96:4 *n*-hexane/*i*PrOH, 20 °C, 220 nm): t_r((+)-**10**) = 18.7, t_r((−)-**10**) = 20.6 min.

Diastereomeric 4-({[*tert*-butyl(diphenyl)silyl]oxy}methyl)-2-methylcyclopent-2-en-1-ols (11, 12): DIBAL (1 M in *n*-hexane, 4.0 mL, 4.0 mmol) was added to a solution of (−)-**7f** (1.29 g, 3.54 mmol) in dry THF (80 mL) at −75 °C under an argon atmosphere. After the reaction mixture had been stirred for 35 min, TLC analysis indicated complete conversion. Water (1.6 mL) and silica (8 g) were added, and the mixture was allowed to warm to RT. The mixture was filtered through Celite and washed with ethyl acetate. The solvent was removed in vacuo and the residue was subjected to flash chromatography on silica (100 g, petroleum ether/ethyl acetate 10:1 to 3:1). The stereoisomeric products were isolated as colorless oils, (−)-**11** (1.04 g, 80 %) and (−)-**12** (0.23 g, 15 %).

*Compound (−)-(1*R*,4*S*)-**11***: R_f(**11**) = 0.27 (petroleum ether/ethyl acetate 3:1); $[\alpha]_D^{20} = -40.6$ ($c = 0.66$ in MeOH); ^{1}H NMR (500 MHz, $CDCl_3$): $\delta =$ 7.67–7.64 (m, 4H; Ar), 7.45–7.37 (m, 6H; Ar), 5.36 (s, 1H; CH=), 4.38 (m, 1H; C*H*OH), 3.61–3.55 (m, 2H; OCH_2), 2.74–2.70 (m, 1H; C*H*CH=), 2.41 (ddd, $J = 14.6$, 7.5, 7.5 Hz, 1H; CH_2CHOH), 2.35 (d, $J = 9.8$ Hz, 1H; OH), 1.84 (s, 3H; CH_3), 1.61 ppm (ddd, $J = 13.8$, 2.6, 2.6 Hz, 1H; CH_2CHOH), 1.05 ppm (s, 9H; *t*Bu); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta =$ 144.4 (s; CH=*C*), 135.9, 135.8 (2d; Ar), 133.5, 133.4 (2s; Ar), 129.9 (d, Ar), 128.7 (d; *C*H=), 127.9, 127.8 (2d; Ar), 78.9 (d; *C*HOH), 66.6 (t; OCH_2), 45.8 (d; *C*HCH=), 38.1 (t; CH_2CHOH), 27.0 (q; $C(CH_3)_3$), 19.4 (s; *C*$(CH_3)_3$), 14.0 ppm (q; CH_3); HRMS (FAB): *m*/*z*: calcd for $C_{23}H_{30}O_2SiNa$: 389.1913; found: 389.1886 [*M*+Na]$^+$; elemental analysis calcd (%) for $C_{23}H_{30}O_2Si$: C 75.36, H 8.25; found: C 75.07, H 8.29.

*Compound (−)-(1*S*,4*S*)-**12***: $[\alpha]_D^{20} = -96$ ($c = 1.08$ in MeOH); ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 7.67$–7.63 (m, 4H; Ar), 7.44–7.36 (m, 6H; Ar), 5.51 (s, 1H; CH=), 4.63–4.60 (m, 1H; C*H*OH), 3.52 (d, $J = 6.4$ Hz; 2H; OCH_2), 3.00–2.96 (m, 1H; C*H*CH=), 2.07 (ddd, $J = 13.9$, 7.3, 4.2 Hz, 1H; CH_2CHOH), 1.82 (ddd, $J = 13.9$, 8.0, 3.7 Hz, 1H; CH_2CHOH), 1.79 (s, 3H; CH_3), 1.04 ppm (s, 9H; *t*Bu); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 143.3$ (s; CH=*C*), 135.8, 135.7 (2d; Ar), 134.1, 134.0 (2s; Ar), 130.3 (d; CH=), 129.7, 129.7, 127.7 (3d; Ar), 79.7 (d; *C*HOH), 67.8 (t; OCH_2), 46.1 (d; *C*HCH=), 37.9 (t; CH_2CHOH), 27.0 (q; $C(CH_3)_3$), 19.4 (s; *C*$(CH_3)_3$), 13.8 ppm (q; CH_3); HRMS (FAB): *m*/*z*: calcd for $C_{23}H_{29}OSi$: 349.1988; found: 349.1964 [*M*+H−H_2O]$^+$; elemental analysis calcd (%) for $C_{23}H_{30}O_2Si$: C 75.36, H 8.25; found: C 75.50, H 8.22.

(−)-(1*R*,4*S*)-4-({[*tert*-Butyl(diphenyl)silyl]oxy}methyl)-2-methylcyclopent-2-en-1-yl methyl carbonate (13): Under an argon atmosphere, a stirred solution of alcohol (−)-**11** (2.60 g, 7.10 mmol) and pyridine (2.3 mL, 28 mmol) in dry CH_2Cl_2 (110 mL) was cooled to 0 °C. Methyl chloroformate (2.2 mL, 28 mmol) was added dropwise, and the mixture was allowed to warm to RT over a period of 16 h (monitored by TLC: R_f(**11**) = 0.31, petroleum ether/ethyl acetate 5:1). A saturated aqueous so-

lution of NH_4Cl was added (100 mL) to the reaction mixture. The phases were separated and the aqueous phase was extracted with CH_2Cl_2 (2× 100 mL). The combined organic phases were washed with a saturated aqueous solution of $CuSO_4$ (100 mL) and brine (100 mL). The organic phase was dried over Na_2SO_4, and the solvent was removed in vacuo. The crude product was purified by flash chromatography on silica (30 g, petroleum ether/ethyl acetate 5:1) to yield (−)-**13** (2.60 g, 86%) as a colorless oil. R_f(**13**) = 0.56 (petroleum ether/ethyl acetate 5:1); $[\alpha]_D^{20} = -61$ (c = 0.46 in MeOH, 98% *ee*); ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.68–7.64 (m, 4H; Ar), 7.45–7.34 (m, 6H; Ar), 5.63–5.61 (m, 1H; CH=), 5.47–5.43 (m, 1H; C*H*OCO$_2$CH$_3$), 3.78 (s, 3H; OCH$_3$), 3.63–3.52 (m, 2H; OCH$_2$), 2.85–2.75 (m, 1H; C*H*CH=), 2.54 (ddd, J = 14.3, 7.8, 7.8 Hz, 1H; CH_2CHOCO$_2$CH$_3$), 1.74 (s, 3H; CCH$_3$), 1.60 (ddd, J = 14.3, 4.7, 4.7 Hz, 1H; CH_2CHOCO$_2$CH$_3$), 1.06 ppm (s, 9H; *t*Bu); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 156.0 (s; C=O), 139.0 (s; CH=*C*), 135.8, 135.7, (2d; Ar), 134.1, 134.0 (2s; Ar), 132.4 (d; CH=), 129.7, 127.8 (2d; Ar), 85.4 (d; *C*HOCO$_2$CH$_3$), 68.0 (t; OCH$_2$), 54.7 (q; OCH$_3$), 46.2 (d; *C*HCH=), 34.3 (t; *C*H$_2$CHOCO$_2$CH$_3$), 27.0 (q; C(*C*H$_3$)$_3$), 19.4 (s; *C*(CH$_3$)$_3$), 13.9 ppm (q; CH$_3$); HRMS (FAB): m/z: calcd for $C_{23}H_{29}OSi$: 349.1988; found: 349.1995 [M+H−MeOCOOH]$^+$; elemental analysis calcd (%) for $C_{25}H_{32}O_4Si$: C 70.72, H 7.60; found: C 70.79, H 7.66.

(−)-9-[(1*R*,4*S*)-4-({[*tert*-Butyl(diphenyl)silyl]oxy}methyl)-2-methylcyclopent-2-en-1-yl]-6-chloro-9*H*-purine-2-amine (14): A solution of 2-amino-6-chloropurine (596 mg, 3.50 mmol) in dry DMSO (10 mL) was added to a solution of (−)-**13** (1.247 g, 2.93 mmol) and [Pd(PPh$_3$)$_4$] (348 mg, 0.300 mmol) in dry THF (12 mL) at RT under an argon atmosphere. The mixture was stirred at RT until conversion was complete (18 h; monitored by TLC, R_f(**13**) = 0.67, CH_2Cl_2/methanol 9:1). Water (20 mL) was added and the mixture was extracted with ethyl acetate (4×30 mL). The organic phase was dried over Na_2SO_4, and the solvent was removed in vacuo. The crude product was subjected to flash chromatography on silica (170 g, CH_2Cl_2/methanol 99:1) to yield a mixture of the regioisomers **14** and **15** (1.10 g, 72% combined yield) in a ratio of 86:14 (determined by ^{1}H NMR spectroscopy).

An analytically pure fraction of the major product (−)-**14** was obtained by preparative HPLC (column: Latek, 250×21 mm, 5 μ silica; CH_2Cl_2/methanol 99.5:0.5, 20 mL min^{-1}, 50 bar) as a colorless foam. The analytical data refers to this sample. $[\alpha]_D^{20} = -49.5$ (c = 0.49 in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.67–7.62 (m, 5H; Ar), 7.46–7.34 (m, 6H; Ar), 5.76–5.75 (m, 1H; CH=), 5.38 (ddd, J = 8.6, 6.8, 1.0 Hz, 1H; CH$_2$C*H*N), 5.01 (s, 2H; NH$_2$), 3.74–3.62 (m, 2H; OCH$_2$), 3.02–2.93 (m, 1H; C*H*CH=), 2.72 (ddd, J = 13.9, 8.6, 8.6 Hz, 1H; CH_2CHN), 1.71 (ddd, J = 13.6, 6.6, 6.6 Hz, 1H; CH_2CHN), 1.55 (s, 3H; CH$_3$), 1.06 ppm (s, 9H; *t*Bu); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 159.0, 154.0, 151.3 (3s; purine), 140.9 (d; purine), 137.8 (s; Ar), 135.7 (d; Ar), 133.6 (s; Ar), 133.1 (d; CH=), 129.9, 127.9 (2d; Ar), 125.7 (s; =*C*CH$_3$), 67.2 (t; OCH$_2$), 62.1 (d; CH$_2$*C*HN), 46.5 (d; *C*HCH=), 35.4 (t; *C*H$_2$CHN), 27.1 (q; C(*C*H$_3$)$_3$), 19.4 (s; *C*(CH$_3$)$_3$), 13.8 ppm (q; CH$_3$); HRMS (FAB): m/z: calcd for $C_{28}H_{33}ClN_5OSi$: 518.2143; found: 518.2163 [M+H$^+$]; elemental analysis calcd (%) for $C_{28}H_{32}{}^{35}ClN_5OSi$: C 64.91, H 6.23, N 13.52, Cl 6.84; found: C 64.61, H 6.21, N 13.25, Cl 6.89.

(+)-[(1*S*,4*R*)-4-(2-Amino-6-chloro-9*H*-purine-9-yl)-3-methylcyclopent-2-en-1-yl]methanol (16) and (−)-[(1*S*,2*S*)-2-(2-amino-6-chloro-9*H*-purin-9-yl)-3-methylcyclopent-3-en-1-yl]methanol (17): A solution of the mixture of **14** and **15** (604 mg, 1.17 mmol), described above, in dry THF (25 mL) was treated with a solution of HF in pyridine (ca. 70% HF/30% pyridine, 2.3 mL, 2.5 g, ≈90 mmol HF) in a Teflon flask. Conversion was complete after the reaction mixture had been stirred for 2.5 h at RT (monitored by TLC: R_f(**15**) = 0.52, CH_2Cl_2/methanol 95:5). Aqueous Na_2CO_3 (2 M, 20 mL) was added dropwise. The mixture was extracted with ethyl acetate (3×30 mL), and the organic phase was dried over Na_2SO_4. The solvent was removed in vacuo and the crude product was subjected to flash chromatography on silica (8 g, CH_2Cl_2/methanol 95:5) to yield a mixture of the regioisomers **16** and **17** (233 mg, 72%). The isomers were separated by preparative HPLC (50 mg per run; column: Latek, 250×21 mm, 5 μ silica; CH_2Cl_2/methanol 97:3, 20 mL min^{-1}, 50 bar). Both compounds were obtained as colorless solids: (+)-**16** (163 mg, 50%) and (−)-**17** (32 mg, 11%).

*Compound (+)-(1*S*,4*R*)-**16***: Crystallization of (+)-**16** by slow evaporation from ethanol at RT yielded colorless, plate-shaped crystals. $[\alpha]_D^{20} = +3.0$ (c = 0.28 in MeOH); m.p. 180–184 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.85 (s, 1H; HC=N), 5.76–5.73 (m, 1H; CH=C), 5.32–5.25 (m, 1H; CH_2CHN), 5.13 (s, 2H; NH$_2$), 3.85 (dd, J = 10.5, 2.7 Hz, 1H; OCH_aH$_b$), 3.74 (dd, J = 10.6, 3.3 Hz, 1H; OCH$_a$$H_b$), 3.80–3.67 (m, 1H; OH), 3.08–3.02 (m, 1H; C*H*CH$_2$OH), 2.81 (ddd, J = 14.5, 9.5, 9.5 Hz, 1H; CH$_2$C*H*N), 2.14 (ddd, J = 14.5, 5.6, 5.6 Hz, 1H; CH_2CHN), 1.53 ppm (s, 3H; CH$_3$); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 158.6, 153.1, 151.9 (3s; purine), 142.4 (d; purine), 138.3 (s; purine), 132.7 (d; CH=), 126.1 (s; CH=*C*), 65.3 (t; OCH$_2$), 64.4 (d; CH$_2$*C*HN), 46.4 (d; *C*HCH$_2$OH), 33.0 (t; *C*H$_2$CHN), 13.8 ppm (q; CH$_3$); HRMS (FAB): m/z: calcd for $C_{12}H_{15}{}^{35}ClN_5O$: 280.0965; found: 280.0967 [M+H$^+$].

*Compound (−)-(1*S*,2*S*)-**17***: Crystallization of (−)-**17** by slow evaporation at RT from methanol yielded colorless needles. $[\alpha]_D^{20} = -25.4$ (c = 0.18 in MeOH); m.p. 192–194 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.55 (s, 1H; HC=N), 6.01 (s, 1H; CH=), 5.28 (s, 2H; NH$_2$), 5.20 (d, J = 6.4 Hz, 1H; CCHN), 3.50–3.30 (m, 2H; OH, OCH$_2$), 3.05–2.94 (m, 1H; OCH$_2$), 2.93–2.80 (m, 1H; C*H*CH$_2$OH), 2.45 (dddd, J = 16.6, 7.5, 2.8, 1.7 Hz, 1H; CH_2CH=), 2.15–2.03 (m, 1H; CH_2CH=), 1.75 ppm (s, 3H; CH$_3$); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 159.0, 154.0, 152.1 (3s; purine), 141.4 (d; purine), 136.7 (s; CH=*C*), 133.3 (d; CH=), 126.0 (s; C-purine), 63.2 (d; CHN), 60.9 (t; OCH$_2$), 47.4 (d; *C*HCH$_2$OH), 29.8 (t; *C*H$_2$CH=), 14.9 ppm (q; CH$_3$); HRMS (FAB): m/z: calcd for $C_{12}H_{15}{}^{35}ClN_5O$: 280.0965; found: 280.0934 [M+Na$^+$].

(+)-2-Amino-9-[(1*R*,4*S*)-4-(hydroxymethyl)-2-methylcyclopent-2-en-1-yl]-1,9-dihydro-6*H*-purine-6-one (2′-Methylcarbovir) (18): A solution of (+)-(1*S*,4*R*)-**16** (40.5 mg, 0.145 mmol) in aqueous NaOH (0.5 M, 2 mL) was heated at reflux for 30 min, when conversion was complete (monitored by TLC) saturated aqueous $NaHCO_3$ (2 mL) was added. The mixture was concentrated in vacuo, and the residue was subjected to flash chromatography on silica (15 g, CH_2Cl_2/methanol 95:5) to yield (+)-(1*R*,4*S*)-2′-methylcarbovir (**18**) (31 mg, 82%) as a colorless solid. With the exception of the optical rotation, the analytical data matched the data provided by Crimmins et al.[25b] R_f(**18**) = 0.02, (CH_2Cl_2/methanol 95:5); m.p. >250 °C; $[\alpha]_D^{20} = +10.4$ (c = 0.11 in MeOH) (lit.:[25b] $[\alpha]_D$ = −61.0 (c = 0.31 in MeOH)); ^{1}H NMR (300 MHz, [D$_6$]DMSO): δ = 10.58 (s, 1H; NH), 7.59 (s, 1H; HC=N), 6.44 (s, 2H; NH$_2$), 5.70 (dd, J = 2.8, 1.2 Hz, 1H; CCH=), 5.22–5.16 (m, 1H; CCHN), 4.68 (t, J = 5.2 Hz, 1H; OH), 3.43 (dd, J = 5.5, 5.5 Hz, 2H; OCH$_2$), 2.82–2.73 (m, 1H; C*H*CH$_2$OH), 2.58 (ddd, J = 13.7, 8.9, 8.8 Hz, 1H; CH_2CHN), 1.65 (ddd, J = 13.7, 5.8, 5.8 Hz, 1H; CH_2CHN), 1.48 ppm (s, 3H; CH$_3$); ^{13}C NMR (75 MHz, [D$_6$]DMSO): δ = 156.8, 153.5, 151.1, 137.7 (4s), 135.3 (d; purine), 132.1 (d; CH=), 116.4 (s; CH=*C*), 64.3 (t; OCH$_2$), 60.8 (d; CHN), 46.3 (d; *C*HCH$_2$OH), 34.7 (t; *C*H$_2$CHN), 13.4 ppm (q; CH$_3$); HRMS (FAB): m/z: calcd for $C_{12}H_{16}N_5O_2$: 262.1304; found: 262.1325 [M+H]$^+$; HPLC (Daicel AD-H column, 60:40 *n*-hexane/*i*PrOH, 30 °C, 254 nm): t_r((1*S*,4*R*)-**18**) = 13, t_r((1*R*,4*S*-**18**) = 16 min, 97.5% *ee*.

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