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Enantioselective Synthesis of the $C_{10}-C_{20}$ Fragment of Fusicoccin A

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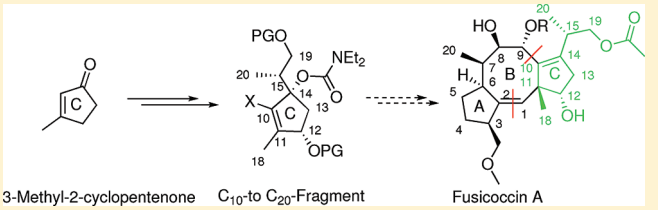
Supporting Information

ABSTRACT: A synthesis of the fully protected C-ring fragment of the tricyclic diterpene fusicoccin A is reported. The desired cyclopentenyl halides **5a**,**b** are obtained in a total of nine steps. Key transformations of the synthesis sequence are a nonconventional Cr-catalyzed allylic oxidation of a protected intermediate cylcopentenone, a diastereoselective addition of a propenyl Grignard/$CeCl_3$ reagent to the unmasked cyclopentenone, and an asymmetric hydroboration of the isopropenyl substituent. The protected and suitably functionalized C-ring fragment paves the way to explore further the total synthesis of fusicoccin A.



INTRODUCTION

The glycosylated phytotoxic diterpene fusicoccin A (Scheme 1) isolated from the fungus *Fusicoccum amygadaly*[1] stabilizes the protein−protein interaction between the autoinhibitory region of the plant plasma membrane H^+-ATPase and a 14−3−3 protein.[2−4] 14−3−3 proteins may be attractive targets for new drug discovery programs, since these conserved adapter proteins[5] play important roles in the regulation of numerous pharmacologically relevant proteins.[6,7] Notably, fusicoccin A induces apoptosis in a wide panel of human cancer cell lines in combination with interferon-α treatment.[8] Other representatives of the fusicoccane family, in particular cotylenin A, induce differentiation in murine and human myeloid leukemia cell,[9,10] and in combination with rapamycin cotylenin A causes growth arrest in breast carcinoma MCF-7 cells.[11] Kato et al. succeeded in the synthesis of the related natural products albolic acid and ceroplastol II and established a route to cotylenol.[12−14] However, a total synthesis of fusicoccin A has not been reported. For the synthesis of the central 5−8−5-membered scaffold characteristic for the fusicoccines, several methods have been reported.[15−18] Herein, we outline a possible approach toward fusiccocin A and describe the enantioselective synthesis of its C-ring fragment.

RETROSYNTHETIC ANALYSIS

In planning the fusicoccin synthesis, we envisaged formation of the highly decorated eight-membered B-ring as the crucial step (Scheme 1). It was planned to employ an 8-endo radical cyclization induced by samarium(II)[19,20] for this purpose.

Addition of a radical generated from an appropriately placed aldehyde to a double bond embedded in the five-membered C-ring and concomitant loss of a leaving group at C(14) would simultaneously install the C(10)−C(14) double bond in one step. The stereochemical outcome of this transformation should be controlled by chelation of samarium. Accordingly, the C(1)−C(11) bond was disconnected to yield the fully functionalized linear precursor **1**.

The configuration at C(14) and the choice of the leaving group were considered to be crucial, and we chose a stable carbamate as leaving group that would release CO_2 upon cylization. The precursor **1** was traced back to the A-ring fragment **2** and the C-ring fragment **3**. Coupling of these fragments by means of a Grignard-type addition should follow the Cram chelate model.[21,22] Alternatively, an asymmetric Nozaki−Hiyama−Kishi reaction could be considered.[23]

We planned to synthesize the C-ring fragment **3** from commercially available 3-methyl-2-cyclopenten-1-one (**6**) as shown in Scheme 1. The synthesis plan included establishment of the stereochemistry at C(14) by means of a Grignard addition[24] to the carbonyl group of intermediate **5** anti to the substituent at C(12). For introduction of the required protected alcohol at C(12) in the appropriate configuration, we envisioned an allylic oxidation/reduction strategy.

RESULTS AND DISCUSSION

Synthesis of Cyclopentenones 5 by Allylic Oxidation and Enantioselective Reduction. The synthesis of cyclopentenones **5a**,**b** involved halogenation of the unsaturated cyclic ketone **6**, allylic oxidation, enantioselective reduction, and protection/deprotection steps (Scheme 2).

Halogenation of **6** employing established procedures, e.g. addition of the corresponding halogen to the enone and subsequent elimination,[25,26] gave vinyl halides **7a**,**b** in low yields.

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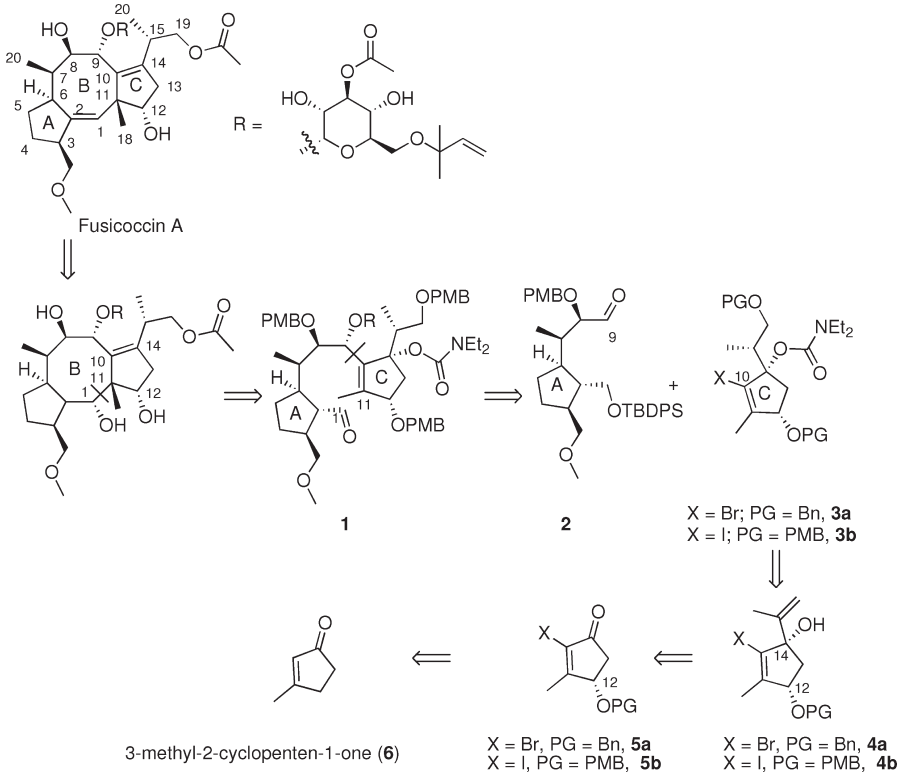
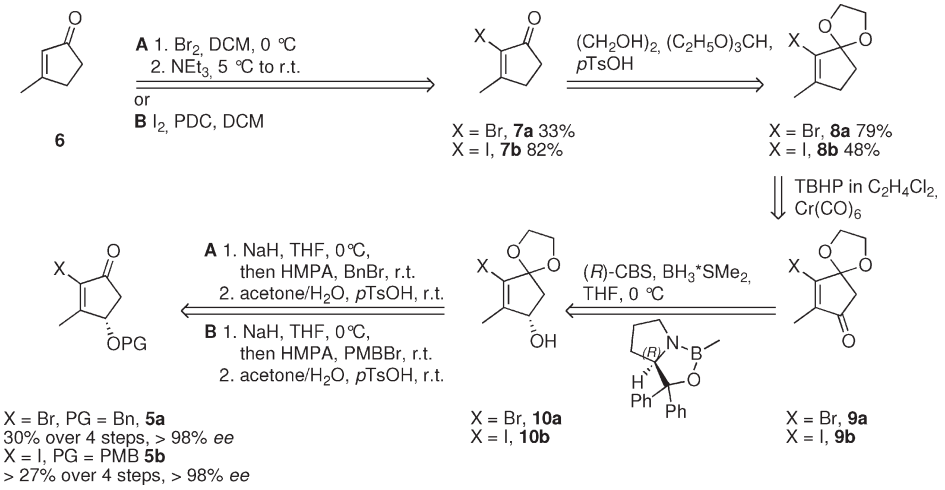
Scheme 1. Retrosynthetic Analysis of Fusicoccin A and of Its Fully Protected C-Ring Fragment



Scheme 2. Synthesis of Chiral Cyclopentenones 5a,b



As an alternative, iodination using iodine and substoichiometric amounts of pyridinium dichromate[27] was employed, which gave **7b** in high yield. To allow for regioselective allylic oxidation, the keto group of intermediates **7** was protected as a cyclic acetal.[25,28] Allylic oxidation with selenium dioxide[29] often yields mixtures of racemic alcohol and the desired ketone, which may be hard to separate and the ketal group is acid-sensitive. Therefore, this oxidant and transformations proceeding under acidic conditions were not considered. For selective allylic oxidation of olefin **8a** several established methods were explored, which are summarized in Table 1 of the Supporting Information. In the majority of the cases decomposition, deprotection of the carbonyl compound, or only partial conversion was observed. The best results were achieved by employment of a solution of TBHP in dichloroethane as modification of Pearson's chromium-catalyzed oxidation method.[30] With this reagent oxidation of **8a,b** proceeded in preparatively viable yields of up to 74% and without substantial formation of byproduct.

Due to the sensitivity of **9a,b**, the crude oxidation products were directly subjected to enantioselective reduction,[31] using the

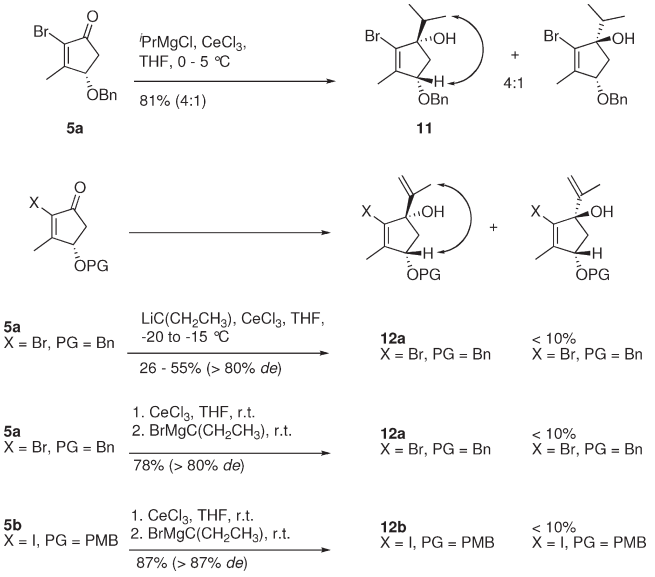
CBS catalyst and borane, yielding the allylic alcohols **10a,b** with high enantiomeric excess (>98% ee). The absolute configuration of the allylic alcohols was confirmed by Mosher ester analysis,[32] which revealed that reduction using (*S*)-(−)-2-methyloxazaborolidine resulted in the formation of the *R* alcohol. This result is in agreement with the expected transition state for the CBS reduction. Protection of the alcohol group either as benzyl ether or as *p*-methoxybenzyl ether and subsequent cleavage of the ketal using acetone/water and *p*-TsOH gave the desired building blocks **5a,b** in 30% yield over four steps from ketones **7**.

Syntheses of Cyclopentenes 3a,b. For establishment of the quaternary stereocenter at C(14), initially the Grignard addition of isopropylmagnesium chloride[24] to the carbonyl group of **5a** promoted by $CeCl_3$ was explored. Thereby compound **5a** was converted into the two separable diasteromers of the cotylenin building block, which were formed in a ratio of 4:1 in favor of the desired diastereomer **11** (Scheme 3). Under comparable conditions **5b** only underwent halogen/metal exchange. In order to introduce the correctly configured side chain of fusicoccin, the use of an organometallic isopropenyl reagent was investigated. Isopropenyllithium,[24] generated in situ,[33] adds to **5a** anti to the protected alcohol with an appreciable selectivity of 9:1; however, yields were not reproducible (Scheme 3). In contrast, the reagent obtained from isopropenylmagnesium bromide[34] and $CeCl_3$ reliably gave **12a,b** in high yield and with high diasteroselectivity (Scheme 3). The configuration of all products of the Grignard-type addition reactions, shown in Scheme 3, was verified by NOESY experiments. Observed NOE signal enhancements are highlighted by arrows, indicating that the nucleophiles preferably add anti to the protected alcohol at C(12) of the cyclopentyl ring.

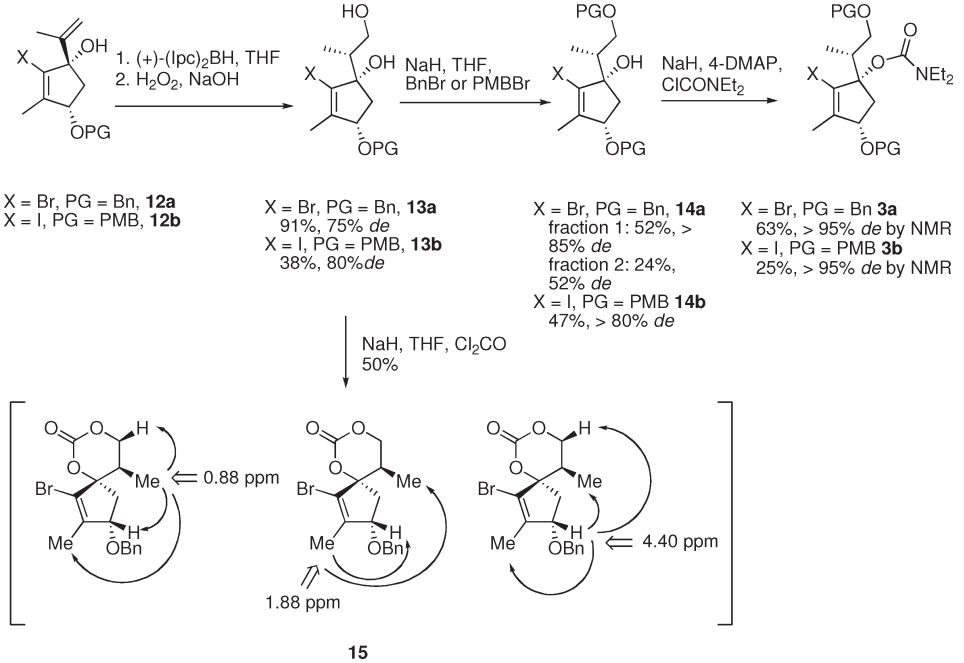
For completion of the synthesis of the C-ring fragment, **12a,b** were subjected to asymmetric hydroboration with (+)-$(Ipc)_2BH$[35] and alcohols **13a,b** were obtained with 75% and 80% de, respectively (Scheme 4). The configuration of the hydroboration product **13a** was determined by means of NMR investigations. For conclusive analysis, diol **13a** was converted to the structurally more rigid carbonate **15.** Subsequent NOE experiments (signal enhancements are indicated by arrows in Scheme 4) revealed that the desired product was formed. Notably, the use of (−)-isopinocampheylborane as hydroborating agent led to reduction but not to reversal of stereoselectivity. This finding indicates that the hydroboration is not reagent- but substrate-controlled. The use of 9-BBN as hydroborating agent did not lead to product formation.

Subsequent selective protection of the primary alcohol by *O*-alkylation and, finally, establishment of the quaternary diethylcarbamate yielded fully functionalized fragments **3a,b** with >95% diastereomeric purity.

Scheme 3. Addition of Isopropyl and Isopropenyl Reagents to Halovinyl Ketones 5a,b



Scheme 4. Synthesis of Fully Functionalized C-Ring Fragments 5a,b and 1D-NOE Experiments of 15



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In conclusion, we have developed a highly stereoselective synthesis of the C-ring fragment of fusicoccin A. The desired vinyl halides **3a**,**b** were obtained in a total of nine steps. Key transformations of the reaction sequence are a nonconventional Cr-catalyzed allylic oxidation using *tert*-butylhydroperoxide in dichloromethane, a diastereoselective Grignard addition, and an asymmetric hydroboration with diisopinocampheylborane. The availability of these fragments opens up the opportunity to further investigate the total synthesis of fusicoccin A.

EXPERIMENTAL SECTION

Reagents, solvents, and the starting materials were purchased from commercial sources. All reactions were carried out using anhydrous solvents and under an inert gas atmosphere unless otherwise specified. THF and methanol were purchased as anhydrous solvents in Sure-Seal bottles and used without any further treatment. DCM was freshly distilled over calcium hydride. ^{1}H and ^{13}C NMR and NOESY spectra were acquired on a 400, 500, or 600 MHz machine. Chemical shifts are reported in ppm (δ), and the coupling constants are given in Hz (J). NMR peak assignments are based on 2D NMR experiments (COSY, TOCSY, HSQC, HMBC). Numbering of the fusicoccin scaffold in Scheme 1 was employed for signal assignment. The sample concentration c is given in g/100 mL for the measurement of the optical rotations. Chiral GC chromatograms were recorded to calculate ee values.

Preparation of 2-Bromo-3-methyl-2-cyclopentenone (7a)[25,28]. Under argon a solution of 3.70 mL of bromine (73.2 mmol, 1.10 equiv) in 60.0 mL of DCM was added to a solution of 6.40 g of 3-methyl-2-cyclopentenone (**6**; 66.5 mmol, 1.00 equiv) in 70.0 mL of DCM within 45 min while the temperature was kept below 5 °C. The mixture was stirred until nearly complete decoloration (2 h); 13.7 mL of triethylamine was added at 5 °C, and the reaction mixture was stirred overnight at room temperature. To the resulting black mixture was added 30.0 mL of 1.00 M HCl carefully. After stirring for 30 min, the layers were separated and the aqueous layer was extracted once with DCM. The combined organic layers were washed with saturated $NaHCO_3$ solution and brine, dried over $MgSO_4$, and concentrated in vacuo. Distillation under reduced pressure (0.7−1.2 mbar, oil bath temperature 90−110 °C, bp 70 °C) yielded 5.30 g of a pale yellow solid. Recrystallization from pentane delivered 3.70 g of the desired product (20.9 mmol, 33%) as colorless crystals. R_f = 0.35 (cyclohexane/EtOAc 7/3). Mp: 53.5 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.67−2.65 (m, 2H, H-13), 2.57−2.53 (m, 2H, H-12), 2.81 (s, 3H, H-18) ppm. ^{13}C NMR (100.7 MHz, $CDCl_3$): δ 201.5 (C_q, C14), 173.4 (C_q, C11), 123.4 (C_q, C10), 33.5 (CH_2, C13), 32.4 (CH_2, C12), 19.1 (CH_3, C18) ppm. HRMS (EI): m/z calcd for $[C_6H_7OBr]^+$ 173.9675, obsd 173.9674; calcd for $[C_6H_7O^{81}Br]^+$ 175.9654, obsd 175.9654.

Preparation of 6-Bromo-7-methyl-1,4-dioxaspiro[4.4]non-6-ene (8a)[25,28]. To a solution of 21.7 g (124.2 mmol, 1.00 equiv) of **10** under argon in 73.4 mL of triethyl orthoformate (434.7 mmol, 3.50 equiv) were added 48.5 mL of ethylene glycol (869.5 mmol, 7.00 equiv) and 236 mg of *p*-toluenesulfonic acid (1.24 mmol, 0.01 equiv). The reaction mixture was stirred at room temperature until the starting material was completely consumed (GC/MS, 15 h). Water was added, and the mixture was extracted three times with cyclohexane. The combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated in vacuo. After distillation over K_2CO_3 under reduced pressure (0.7−0.9 bar, oil bath temperature 85−95 °C, bp 60−65 °C) 21.5 g (97.9 mmol, 79%) of a colorless wax was obtained. ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.18 (m, 2H, CH_2-ketal), 3.98 (m, 2H, CH_2-ketal), 2.35 (m, 2H, H-12), 2.17 (m, 2H, H-13), 1.80 (s, 3H, H-18) ppm. ^{13}C NMR (100.7 MHz, $CDCl_3$): δ 144.6 (C_q, C11), 141.9 (C_q, C14), 119.3 (C_q, C10), 66.0 (2CH_2, 2C-ketal), 34.7 (CH_2, C13), 33.1 (CH_2, C12), 16.7 (CH_3, C18) ppm. HRMS (EI): m/z calcd for $[C_8H_{11}O_2Br]^+$ 217.9937, obsd 217.9928; calcd for $[C_8H_{11}O_2{}^{81}Br]^+$ 219.9922, obsd 219.992 06.

9-Bromo-8-methyl-1,4-dioxaspiro[4.4]non-8-en-7-one (9a). 6-Bromo-7-methyl-1,4-dioxaspiro[4.4]-non-6-ene (**8a**; 11.5 g, 52.3 mmol, 1.00 equiv) was dissolved in 130 mL of a 29% solution of TBHP in $C_2H_4Cl_2$ (523 mmol, 10.0 equiv) under an inert gas atmosphere, and molecular sieves (4 Å) were added. $Cr(CO)_6$ (1.20 g, 5.32 mmol, 0.50 equiv) was added, and the reaction mixture was stirred under argon at 40 °C for 48 h and for an additional 2 days at room temperature (GC/MS analysis indicated complete conversion). The reaction mixture was filtered and washed with EtOAc. The filtrate was diluted with water and extracted three times with EtOAc. The combined organic layers were washed with brine, dried over $MgSO_4$, and evaporated to dryness. The resulting dark green oil was dissolved in EtOAc and filtered over Celite. The solvent was evaporated to yield 7.10 g of a slightly yellow wax as the crude desired product (30.5 mmol, 58%). An analytically pure sample of **9a** was obtained by column chromatography on deactivated silica gel (cyclohexane/EtOAc 9:1). R_f = 0.42 (cyclohexane/EtOAc 7/3). IR (ATR): 2976 (w), 2956 (w), 2912 (m), 2890 (w), 2845 (w), 1668 (m), 1471 (m), 1440 (m) cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$ filtered over basic Al_2O_3): δ 4.29 (m, 2H, CH_2-ketal), 4.09 (m, 2H, CH_2-ketal), 2.78 (s, 2H, H-13), 1.84 (s, 3H, H-18) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$ filtered over basic Al_2O_3): δ 199.4 (C_q, C12), 152.8 (C_q, C14), 145.0 (C_q, C11), 110.5 (C_q, C10), 66.8 (CH_2, 2C-ketal), 47.6 (CH_2, C13), 10.1 (CH_3, C18) ppm. HRMS (EI): m/z [M]$^+$ calcd for $[C_8H_9O_3{}^{79}Br]^+$ 231.9730, obsd 231.9725; calcd for $[C_8H_9O_3{}^{81}Br]^+$ 233.9709, obsd 233.9704.

(*S*)-9-Bromo-8-methyl-1,4-dioxaspiro[4.4]non-8-en-7-ol (10a). A solution of (*R*)-2-methyl-CBS-oxazaborolidine in THF (3.00 mL, 1.00 M, 3.05 mmol, 0.10 equiv) was transferred under positive argon pressure to a flame-dried two-necked round-bottom flask containing 58.0 mL of THF. After the solution was cooled to 0 °C, dimethyl sulfide−borane complex (5.80 mL, 60.9 mmol, 2.00 equiv) was added dropwise and the mixture was stirred for 20 min at 0 °C. A solution of **9a** (7.10 g, 30.4 mmol, 1.00 equiv) in 30.0 mL of THF was added at 0 °C over a period of 3.5 h using a syringe pump, and the reaction mixture was stirred for 1.5 h at 0 °C. Methanol was added carefully, and the quenched reaction mixture was warmed to room temperature overnight. Water was added, and the mixture was extracted three times with diethyl ether. The combined organic layers were washed with brine and dried over $MgSO_4$, and the solvent was evaporated to dryness to yield 9.50 g of crude **10a** as a pale yellow wax (99% ee by chiral GC). The crude product was used without further purification for the next steps. For analytical purposes 50.0 mg of the crude product was purified by column chromatography on silica gel which had been pretreated with NEt_3 (cyclohexane/EtOAc 9/1 to 7/3) to obtain 24.0 mg of the pure product as a colorless wax. R_f = 0.11 (cyclohexane/EtOAc 7/3). $[\alpha]^{20}_D$ = −20.9° (c = 0.72, $CHCl_3$ filtered over basic Al_2O_3). ^{1}H NMR (400 MHz, $CDCl_3$ filtered over basic Al_2O_3): δ 4.53 (s, br, 1H, H-12), 4.19 (m, 2H, CH_2-ketal), 3.98 (m, 2H, CH_2-ketal), 2.62 (dd, ^2J = 14.1, ^3J = 7.1 Hz, 1H, H-13), 2.02 (dd, ^2J = 14.2, ^3J = 3.4 Hz, 1H, H-13), 1.86 (s, 3H, H-18), 1.75 (s, br, 1H, OH) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$ filtered over basic Al_2O_3): δ 146.3 (C_q, C14), 124.1 (C_q, C11), 115.2 (C_q, C10), 74.5 (CH, C12), 66.3 (CH_2, C-ketal), 65.6 (CH_2, C-ketal), 45.7 (CH_2, C13), 13.6 (CH_3, C18) ppm. HRMS (EI): m/z [M]$^+$ calcd for $[C_8H_{11}O_3{}^{79}Br]^+$ 233.9886, obsd 233.9884; calcd for $[C_8H_{11}O_3{}^{81}Br]^+$ 235.9866, obsd 235.9864.

(*S*)-4-(Benzyloxy)-2-bromo-3-methylcyclopent-2-enone (5a). In a flame-dried two-necked round-bottom flask NaH (3.20 g, 80.7 mmol, 2.00 equiv) was suspended in 150 mL of THF under an argon counterflow. A solution of crude **10a** (9.50 g, 40.3 mmol, 1.00 equiv) in 100 mL of THF was added dropwise over 30 min at

0 °C. The reaction mixture was stirred for 1.5 h at room temperature, HMPA (19.8 mL, 161.3 mmol, 4.00 equiv) and benzyl bromide (9.60 mL, 80.7 mmol, 2.00 equiv) were added, and the mixture was stirred overnight at room temperature. After it was cooled with an ice bath, the mixture was carefully diluted with water and extracted three times with EtOAc. The combined organic layers were washed with brine, dried over $MgSO_4$, and evaporated to dryness to give 25.0 g of crude (*S*)-8-(benzyloxy)-6-bromo-7-methyl-1,4-dioxaspiro[4.4]non-6-ene as a yellow liquid. The crude product was used for the next reaction without further purification: R_f = 0.58 (cyclohexane/EtOAc 7/3).

A solution of 25.0 g of crude (*S*)-8-(benzyloxy)-6-bromo-7-methyl-1,4-dioxaspiro[4.4]non-6-ene and ca. 100 mg of TsOH in 160 mL of acetone/water (25/1) was stirred for 20 h at room temperature and for an additional 4 h at 40 °C until conversion was complete (monitored by GC/MS). The reaction mixture was cooled to room temperature, diluted with water, and extracted three times with EtOAc. The combined organic layers were washed with brine, dried over $MgSO_4$, and evaporated to dryness. Purification by means of column chromatography on silica gel (cyclohexane/EtOAc 9/1) yielded 4.40 g of **5a** (15.5 mmol, 30% over four steps) as a yellow, viscous oil, R_f = 0.52 (cyclohexane/EtOAc 7/3). $[\alpha]^{20}_D$ = 46.4 deg (*c* = 1.13, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.40−7.31 (m, 5H, Ph), 4.67 (d, ^2J = 11.6, 1H, CH_2Ph), 4.58−4.55 (m, 2H, CH_2Ph, H-12), 2.81 (dd, ^2J = 18.1, ^3J = 5.9, 1H, H-13), 2.50 (dd, ^2J = 18.1, ^3J = 1.6, 1H, H-13), 2.19 (s, 3H, H-18) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 197.3 (C_q, C14), 171.0 (C_q, C11), 137.2 (C_q, Ph), 128.8 (2CH, Ph), 128.4 (CH, Ph), 128.1 (2CH, Ph), 126.0 (C_q, C10), 77.6 (CH, C12), 72.2 (CH_2 CH_2Ph), 40.8 (CH_2, C13), 16.3 (CH_3, C18) ppm. HRMS (CI): *m*/*z* $[M + H]^+$ calcd for $[C_{13}H_{14}O_2{}^{79}Br]^+$ 281.0172, obsd 281.0161; calcd for $[C_{13}H_{14}O_2{}^{81}Br]^+$ 283.0151, obsd 283.0142.

(1*S*,4*S*)-4-(Benzyloxy)-2-bromo-1-isopropyl-3-methylcyclopent-2-enol (11). In a flame-dried Schlenk tube a water-free $CeCl_3$ suspension in THF (13.2 mL, 0.10 g/mL, 5.34 mmol, 1.50 equiv; for the preparation see ref 24) was added via a transfer cannula to a solution of isopropylmagnesium chloride in THF (2.76 mL, 2.00 M, 5.34 mmol, 1.50 equiv) at 0 °C under positive argon pressure. The suspension was stirred for 1 h with ice bath cooling, and a solution of **5a** (1.00 g, 3.56 mmol, 1.00 equiv) in 4.00 mL of THF was added dropwise within 25 min under argon. The reaction mixture was stirred at 0 °C until starting material was no longer detectable by GC/MS or TLC (1 h). The reaction mixture was carefully diluted with water and extracted three times with diethyl ether. The combined organic layers were washed with brine, dried over $MgSO_4$, and evaporated to dryness. Purification by column chromatography on silica gel (cyclohexane/EtOAc 9/1) provided 585 mg (1.80 mmol, 51%) of the desired cis isomer **11** as a slightly yellow oil, 181 mg of a diastereomeric mixture, and 131 mg of the pure trans isomer (81% overall yield). Analytical data of the cis isomer **11** are as follows. R_f = 0.58 (cyclohexane/EtOAc 9/1). $[\alpha]^{20}_D$ = +13.6° (*c* = 0.90, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.38−7.33 (m, 4H, Ph), 7.30 (m, 1H, Ph), 4.60 (d, ^2J = 11.7, 1H, CH_2Ph), 4.49 (d, ^2J = 11.7, 1H, CH_2Ph), 4.23 (ddd, ^3J = 7.2, 3.3, ^4J = 0.8, 1H, H-12), 2.49 (dd, ^2J = 14.3, ^3J = 7.2, 1H, H-13), 2.02 (m, 1H, H-15), 1.97 (s, br, 1H, O*H*), 1.84 (d, ^4J = 0.8, 3H, H-18), 1.82 (m, 1H, H-13), 1.03 (d, ^3J = 6.3, 3H, H-19), 0.66 (d, ^3J = 6.8, 3H, H-20) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ 140.5 (C_q, C11), 138.3 (C_q, Ph), 130.5 (C_q, C14), 128.6 (2CH), 127.9 (3CH), 86.73 (C_q, C10), 82.2 (CH, C12), 70.8 (CH_2Ph), 37.9 (CH, C15), 34.3 (CH_2, C13), 17.6 (CH_3, C19/20), 16.4 (CH_3, C19/20), 13.9 (CH_3, C18) ppm. HRMS (CI): *m*/*z* $[M - OH]^+$ calcd for $[C_{16}H_{10}OBr]^+$ 307.0692, obsd 307.0699; calcd for $[C_{16}H_{10}O^{81}Br]^+$ 309.0672, obsd 309.0684. Analytical data of the trans isomer are as follows. R_f = 0.57 (cyclohexane/EtOAc 7/3). $[\alpha]_D{}^{20}$ = −15.8° (*c* = 0.24, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.36 - 1.34 (m, 4H, Ph), 1.29 (m, 1H, Ph), 4.62 (d, ^2J = 11.8, CH_2Ph), 4.52−4.47 (m, 2H, CH_2Ph, H-12), 2.16 (dd, ^2J = 14.1, ^3J = 7.3, 1H. H-13), 2.00−1.94 (m, 2H, H-13, H-15), 1.82 (d, ^4J = 1.0, 3H, H-18), 1.68 (s, br, 1H, O*H*), 1.00 (d, ^3J = 6.8, 3H, H-19), 0.82 (d, ^3J = 6.8, 3H, H-20) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): 141.8 (C_q, C11), 138.4 (C_q, Ph), 129.3 (C_q, C14), 128.6 (2CH), 127.9 (CH), 127.8 (2CH), 87.6 (C_q, C10), 82.3 (CH, C13), 71.4 (CH_2Ph), 37.1 (CH_2, C13), 35.2 (CH, C15), 18.4 (CH_3, C19), 16.3 (CH_3, C20), 14.0 (CH_3, C18) ppm. HRMS (CI): *m*/*z* $[M - OH]^+$ calcd for $[C_{16}H_{20}OBr]^+$ 307.0692, obsd 307.0689; calcd for $[C_{16}H_{20}O^{81}Br]$ 309.0672, obsd 309.0671.

(1*S*,4*S*)-4-(Benzyloxy)-2-bromo-3-methyl-1-(prop-1-en-2-yl)cyclopent-2-enol (12a). In a flame-dried Schlenk tube a water-free $CeCl_3$ suspension in THF (2.63 mL, 0.10 g/mL, 1.07 mmol, 3.00 equiv; for the preparation see ref 24) was added via a transfer cannula to a solution of **5a** (100 mg, 356 μmol, 1.00 equiv) in 5.0 mL of THF under positive argon pressure. The suspension was stirred for 3 h at room temperature, and a solution of isopropylmagensium bromide in THF (2.10 mL, 0.50 M, 1.07 mmol, 3.00 equiv) was added dropwise within 20 min under argon. The reaction mixture was stirred at room temperature until starting material was no longer detectable by GC/MS or TLC (20 min). After it was cooled with an ice bath, the reaction mixture was carefully diluted with water and extracted three times with diethyl ether. The combined organic layers were washed with brine, dried over $MgSO_4$, and evaporated to dryness. Purification by column chromatography on silica gel (cyclohexane/EtOAc 9/1) provided 90.1 mg (279 μmol, 78%, >80% de by NMR) of the desired **12a** as a slightly yellow oil. R_f = 0.45 (cyclohexane/EtOAc 7/3). $[\alpha]^{20}_D$ = −19.1° (*c* = 1.12, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.36−7.34 (m, 4H, Ph), 7.30 (m, 1H, Ph), 5.15 (td, ^4J = 0.8, ^2J = 1.5, 1.5, 1H, H-19), 4.96 (m, 1H, H-19), 4.59 (d, ^2J = 11.8, 1H, CH_2Ph), 4.51 (d, ^2J = 11.8, 1H, CH_2Ph), 4.34 (m, 1H, H-12), 2.61 (dd, ^2J = 13.9, ^3J = 7.2, 1H, H-13), 2.26 (s, br, 1H, O*H*), 2.09 (dd, ^2J = 14.0, ^3J = 4.1, 1H, H-13), 1.87 (d, ^4J = 0.8, 3H, H-18), 1.61 (dd, ^4J = 0.7, 1.4, 3H, H-20) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 146.2 (C_q, C15), 142.0 (C_q, C11), 138.3 (C_q, Ph), 128.6 (2CH, Ph), 128.4 (C_q, C10), 127.9 (CH, Ph), 127.9 (2CH, Ph), 111.6 (CH_2, C19), 86.0 (C_q, C14), 82.2 (CH, C12), 70.8 (CH_2Ph), 43.8 (CH_2, C13), 18.6 (CH_3, C20), 14.0 (CH_3, C18) ppm. HRMS (CI): *m*/*z* $[M - OH]^+$ calcd for $[C_{16}H_{18}O^{79}Br]^+$ 305.0536, obsd 305.0535; calcd for $[C_{16}H_{18}O^{81}Br]^+$ 307.0515, obsd 307.0516.

(1*S*,4*S*)-4-(Benzyloxy)-2-bromo-1-*sec*-butyl-3-methylcyclopent-2-enol (13a). In a flame-dried Schlenk tube freshly prepared (+)-$(Ipc)_2BH$[16] (136 mg, 475 μmol, 2.00 equiv) was suspended in 1.00 mL of THF under positive argon pressure. At 0 °C a solution of **12a** (76.8 mg, 238 μmol, 1.0 equiv) in 500 μL of THF was added dropwise within 5 min. The reaction mixture was stirred for 2.5 h until complete conversion and warmed to room temperature. At 0 °C aqueous NaOH (1.40 mL, 2.00 M, 2.79 mmol, 10.5 equiv) and an aqueous H_2O_2 solution (136 μL, 30%, 1.33 mmol, 5.00 equiv) were added, and stirring was continued for 2 h at room temperature. After addition of water to the mixture it was extracted three times with diethyl ether. The combined organic layers were washed with brine, dried over $MgSO_4$, and evaporated to dryness at room temperature (*caution!* the product is very acid- and temperature-sensitive). After purification by column chromatography on deactivated silica gel (cyclohexane/EtOAc 7/3) 86.9 mg of **13a** was obtained as a colorless oil (217 μmol, 91%). For determination of the diastereomeric excess by means of GC-MS, an analytical sample was dissolved in *N*,*O*-bis(trimethylsilyl)acetamide and the solution stirred at 80 °C for 30 min. de = 75%. R_f = 0.12 (cyclohexane/EtOAc 7/3). $[\alpha]^{20}_D$ = −10.3° (*c* = 1.15, THF). ^{1}H NMR (400 MHz, $CDCl_3$ filtered over basic Al_2O_3): δ 7.38−7.26 (m, 5H, Ph), 4.58 (d, ^2J = 11.8, 1H, CH_2Ph), 4.48 (d, ^2J = 11.8, 1H, CH_2Ph), 4.25 (ddd, ^3J = 7.0, 4.2, ^4J = 0.7, 1H, H-12), 3.79 (m, 1H, H-19), 3.35 (m, 1H, H-19), 2.81 (s, 1H, O*H*), 2.59 (dd, ^3J = 7.0, ^2J = 14.0, 1H, H-13), 2.14 (m, 1H, H-15), 1.93 (dd, ^3J = 4.1, ^2J = 14.0, 1H, H-13), 1.85 (d, ^4J = 0.7, 3H, H-18), 1.78 (m, 1H, O*H*), 0.98 (d, ^3J = 7.0, 3H, H-20) ppm. ^{13}C NMR (100.6 MHz,

$CDCl_3$ filtered over basic Al_2O_3): δ 142.0 (C_q, C11), 138.2 (C_q, Ph), 128.6 (2CH, Ph), 128.4 (C_q, Ph), 127.9 (CH, Ph), 127.9 (2CH, Ph), 85.7 (C_q, C14), 81.5 (CH, C12), 71.0 (CH_2Ph), 65.3 (CH_2, C19), 42.9 (CH, C15), 42.8 (CH_2, C13), 14.0 (CH_3, C18), 11.7 (CH_3, C20) ppm. HRMS (ESI): m/z $[M]^+$ calcd for $[C_{16}H_{21}O_3{}^{79}BrNa]^+$ 363.0566, obsd 363.0566; calcd for $[C_{16}H_{21}O_3{}^{81}BrNa]^+$ 365.0546, obsd 365.0546.

(1*S*,4*S*)-4-(Benzyloxy)-1-((*R*)-1-(benzyloxy)propan-2-yl)-2-bromo-3-methylcyclopent-2-enol (14a). In a flame-dried Schlenk tube NaH (3.60 mg, 60%, 90.6 μmol, 1.50 equiv) was suspended under an argon counterflow in 150 μL of THF at 0 °C. To this suspension was added dropwise a solution of **13a** (20.6 mg, 60.4 μmol, 1.00 equiv) in 150 μL of THF. The mixture was stirred for 20 min at 0 °C, HMPA (23.2 μL, 133 μmol, 2.20 equiv) and benzyl bromide (7.90 μL, 66.4 μmol, 1.10 equiv) were added, and the reaction mixture was stirred for 3 h at room temperature. After cooling with an ice bath, water was added carefully and the mixture was extracted three times with diethyl ether. The combined organic layers were washed with brine, dried over $MgSO_4$, and evaporated to dryness. Column chromatography on deactivated silica gel (cyclohexane/EtOAc 9/1) yielded the desired isomer **14a** (13.5 mg, 52%, >95% de by NMR). Data for the major isomer are as follows. R_f = 0.46 (cyclohexane/EtOAc 7/3). $[\alpha]^{20}{}_D$ = −1.62° (c = 0.56, MeOH). ^{1}H NMR (400 MHz, $CDCl_3$ filtered over basic Al_2O_3): δ 7.36−7.26 (m, 10H, Ph), 4.52 (m, 2H, CH_2Ph), 4.44 (d, ^2J = 11.8, 1H, CH_2Ph), 4.39 (d, ^2J = 11.8, 1H, CH_2Ph), 4.20 (ddd, ^3J = 7.0, 4.4, ^4J = 1.0, 1H, H-12), 3.57 (dd, ^2J = 9.5, ^3J = 6.6, 1H, H-19), 3.26 (m, 1H, H-19), 2.63 (dd, ^2J = 13.8, ^3J = 7.1, 1H, H-13), 2.26 (m, 1H, H-15), 1.91 (dd, ^2J = 13.8, ^3J = 4.4, 1H, H-13), 1.81 (d, ^4J = 1.0, 3H, H-18), 0.99 (d, ^3J = 7.0, 3H, H-20) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$ filtered over basic Al_2O_3): δ 141.6 (2C_q, Ph), 138.4 (C_q, C11), 128.6 (2CH, Ph), 128.5 (2CH, Ph), 128.3 (C_q, C10), 127.8 (6CH, Ph), 85.5 (C_q, C14), 81.5 (CH, C12), 73.5 (CH_2Ph), 72.8 (CH_2, C19), 70.6 (CH_2Ph), 42.9 (CH_2, C13), 40.9 (CH, C15), 13.9 (CH_3, C18), 12.1 (CH_3, C20) ppm. HRMS (ESI): m/z $[M]^+$ calcd for $[C_{23}H_{27}O_3{}^{79}BrNa]^+$ 453.1036, obsd 453.1031; calcd for $[C_{23}H_{27}O_3{}^{81}BrNa]^+$ 455.1015, obsd 455.1010.

(1*S*,4*S*)-4-(Benzyloxy)-1-((*R*)-1-(benzyloxy)propan-2-yl)-2-bromo-3-methylcyclopent-2-enyl Diethylcarbamate (3a). To a solution of **14a** (13.7 mg, 31.7 μmol, 1.00 equiv) in 400 μL of THF in a flame-dried Schlenk tube was added a small amount of NaH (at least 3.00 mg oil free, washed with pentane, ca. 90%, 63.5 μmol, at least 2.00 equiv) under argon pressure. The resulting suspension was stirred for 40 min at room temperature, and small amounts of 4-DMAP and diethylcarbamoyl chloride (44.0 μL, 318 μmol, 10.0 equiv) were added. The reaction mixture was stirred overnight at 60 °C and cooled to room temperature, and water was added. The mixture was extracted three times with EtOAc. The combined organic layers were washed once with brine and evaporated to dryness. The crude product was purified by column chromatography on silica gel which had been pretreated with NEt_3 (cyclohexane/EtOAc 9/1 to 4/1) to yield 10.6 mg of the desired building block **6a** (20.0 μmol, 63%, 95% de by NMR) as a slightly yellow oil. R_f = 0.52 (cyclohexane/EtOAc 7/3). $[\alpha]^{20}{}_D$ = −0.93° (c = 0.48, MeOH). ^{1}H NMR (400 MHz, $CDCl_3$ filtered over basic Al_2O_3): δ 7.34−7.28 (m, 10H, Ph), 4.58 (d, ^2J = 12.1, 1H, CH_2Ph), 4.50 (d, ^2J = 12.1, 1H, CH_2Ph), 4.43 (d, ^2J = 12.1, 1H, CH_2Ph), 4.38 (d, ^2J = 12.1, 1H, CH_2Ph), 4.27 (ddd, ^3J = 7.2, 5.4, ^4J = 1.0, 1H, H-12), 3.43 (dd, ^2J = 9.5, ^3J = 3.7, 1H, H-19), 3.31 (dd, ^2J = 9.5, ^3J = 7.6, 1H, H-19), 3.28−3.15 (m, 4H, CH_2-carbamate), 2.81 (dd, ^2J = 13.6, ^3J = 7.2, 1H, H-13), 2.67−2.55 (m, 2H, H-15, H-13), 1.83 (d, ^4J = 1.0, 3H, H.18), 1.09 (t, ^3J = 7.1, 6H, CH_3-carbamate), 1.05 (d, ^3J = 6.9, 3H, H-20) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$ filtered over basic Al_2O_3): δ 154.0 (C_q, CO), 142.4 (C_q, C11), 138.8 (C_q, Ph), 138.6 (C_q, Ph), 128.5 (4CH, Ph), 127.8 (2CH, Ph), 127.7 (2CH, Ph), 127.6 (2C, C_q, CH, Ph), 123.9 (C_q, C10), 91.3 (C_q, C14), 81.7 (CH, C12), 73.1 (CH_2Ph), 71.3 (CH_2, C19), 70.1 (CH_2Ph), 41.6 (2CH_2-carbamate), 40.5 (CH_2, C13), 40.4 (CH, C15), 13.8 (CH_3-carbamate), 13.8 (CH_3, C18), 13.7 (CH_3-carbamate), 12.9 (CH_3, C20) ppm. HRMS (ESI): m/z $[M]^+$ calcd for $[C_{28}H_{36}O_4N^{79}BrNa]^+$ 552.1720, obsd 552.1715; calcd for $[C_{28}H_{36}O_4N^{81}BrNa]^+$ 554.1700, obsd 554.1693.

Mosher Ester Preparation of ent-10a. *Preparation of (S)-Mosher Ester.* In a flame-dried Schlenk tube 15.0 mg (63.8 μmol, 1.00 equiv) of **ent-10a** together with 16.4 mg (70.2 μmol, 1.10 equiv) of (*S*)-(−)-α-methoxy-α-(trifluoromethyl)phenylacetic acid were dissolved in 1.00 mL of freshly distilled DCM under argon. A 40.8 mg portion (198 μmol, 3.10 equiv) of DCC and 24.2 mg of 4-DMAP (198 μmol, 3.10 equiv) were added, and the reaction mixture was stirred at room temperature for 2 h. Water was added, and the mixture was extracted three times with EtOAc. The combined organic layers were washed with brine, dried over $MgSO_4$, and evaporated. After column chromatography on deactivated silica gel (NEt_3, cyclohexane/EtOAc 9/1) 18.6 mg of the desired (*S*)-Mosher ester (41.2 μmol, 65%) was obtained as a slightly yellow oil: R_f = 0.56 (cyclohexane/EtOAc 7/3). $[\alpha]_D{}^{20}$ = +0.74° (c = 1.27, $CHCl_3$ filtered over basic Al_2O_3). ^{1}H NMR (400 MHz, $CDCl_3$ filtered over basic Al_2O_3) δ 7.53 (m, 2H, Ph), 7.41−7.40 (m, 3H, Ph), 5.70 (dd, 1H, ^3J = 6.9, 3.5, H-12), 4.23−4.16 (m, 2H, CH_2-ketal), 4.20 (m, 1H, CH_2-ketal), 3.96 (m, 1H, CH_2-ketal), 3.55 (s, 3H, OMe), 2.81 (dd, 1H, ^4J = 14.4, ^3J = 7.0, H-13), 2.16 (dd, 1H, ^4J = 14.4, ^3J = 3.6, H-13), 1.66 (s, 3H, H-18) ppm. ^{13}C NMR (100.7 MHz, $CDCl_3$ filtered over basic Al_2O_3): δ 166.5 (C_q, CO), 141.5 (C_q, C11), 132.1 (C_q, Ph), 129.9 (CH, Ph), 128.6 (3CH, Ph), 127.3 (CH, Ph), 126.9 (C_q, CF_3), 115.9 (C_q, C10), 78.0 (CH, C12), 66.5 (CH_2, C-ketal), 66.0 (CH_2, C-ketal), 55.4 (CH_3, OMe), 42.8 (CH_2, C13), 13.5 (C_3, C18) ppm. HRMS (EI): m/z $[M]^+$ calcd for $[C_{18}H_{18}O_5BrF_3]^+$ 450.0290, obsd 450.0280.

Preparation of (R)-Mosher Ester. In a flame-dried Schlenk tube 5.00 mg (21.3 μmol, 1.0 equiv) of **ent-10a** was dissolved in a mixture of 330 μL of $CHCl_3$ and 5.30 μL (65.9 μmol, 3.10 equiv) of pyridine. Under argon 7.50 μL of (*S*)-(+)-α-methoxy-α-(trifluoromethyl)phenylacetyl chloride (40.4 μmol, 1.10 equiv) was added. After stirring at room temperature for 3 h starting material was no longer detectable by TLC. The mixture was diluted with water and extracted three times with diethyl ether. The combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated in vacuo. After column chromatography on deactivated silica gel (NEt_3, cyclohexane/EtOAc 9/1) 5.00 mg (11.1 μmol, 52%) of a slightly yellow oil was obtained: R_f = 0.56 (cyclohexane/EtOAc 7/3), $[\alpha]_D{}^{20}$ = +49.9° (c = 0.39, $CHCl_3$ filtered over basic Al_2O_3). ^{1}H NMR (400 MHz, $CDCl_3$ filtered over basic Al_2O_3): δ 7.51 (m, 2H, Ph), 7.42−7.38 (m, 3H, Ph), 5.71 (ddd, 1H, ^3J = 7.2, 4.0, ^4J = 1.0, H-12), 4.22−4.13 (CH_2, CH_2-ketal), 4.03−3.91 (CH_2, CH_2-ketal), 3.54 (q, 3H, ^4J = 1.2, OMe), 2.79 (dd, 1H, ^2J = 14.3, ^3J = 7.2, H-13), 2.03 (M, 1H, H-13), 1.80 (d, ^4J = 1.0, 3H, H-18) ppm.

Preparation of (3*S*,5*S*,10*R*)-3-(Benzyloxy)-1-bromo-2,10-dimethyl-6,8-dioxaspiro[4.5]dec-1-en-7-one (15). To a solution of 27.0 mg of **14a** (79.1 μmol, 1.0 equiv) in 1.00 mL of THF was added 191 μL of pyridine (2.37 mmol, 30.0 equiv), and the solution was cooled to 0 °C. A solution of 62.4 μL of phosgene in toluene (119 μmol, 1.50 equiv, 20% in toluene) was added. A slightly yellow precipitate formed. The same amount of phosgene was added a second time at 0 °C, and the reaction mixture was stirred for 14 h at room temperature under argon. The reaction was quenched by the addition of saturated $NaHCO_3$ solution, and the mixture was extracted three times with diethyl ether. The combined organic layers were washed once with water and brine, dried over $MgSO_4$, and concentrated in vacuo. After purification by column chromatography on deactivated silica gel (NEt_3, cyclohexane/EtOAc 9/1 to 7/3) 14.7 mg of a slightly yellow oil (40.3 μmol, 51%) was obtained: R_f = 0.3 (cyclohexane/EtOAc 1/1). $[\alpha]_D{}^{20}$ = 57.1° (c = 0.30, THF). ^{1}H NMR (400 MHz, MeOD): δ 7.39−7.33 (m, 4H, Ph), 7.29 (m, 1H, Ph), 4.70 (m, H-19), 4.61 (d, ^2J = 11.8, 1H, CH_2Ph),

4.56 (d, ^2J = 11.8, 1H, CH_2Ph), 4.39 (ddq, ^3J = 7.0, 5.0, ^4J = 0.9, 1H, H-12), 4.27 (dd, ^2J = 11.3, ^3J = 5.8, 1H, H-19), 2.77 (dd, ^2J = 14.0, ^3J = 6.9, 1H, H-13), 2.56 (m, 1H, H-15), 2.27 (dd, ^2J = 14.0, ^3J = 5.0, 1H, H-13), 1.88 (d, ^4J = 1.0, 3H, H-18), 0.87 (d, ^3J = 6.9, 3H, H-20) ppm. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.38−7.29 (m, 5H, Ph), 4.75 (m, 1H, H-19), 4.54 (dd, ^2J = 11.9, 1H, CH_2Ph), 4.51 (dd, ^2J = 11.9, 1H, CH_2Ph), 4.29 (m, 1H, H-12), 4.16 (dd, ^2J = 11.3, ^3J = 5.8, 1H, H-19), 2.56 (dd, ^2J = 14.0, ^3J = 6.9, 1H, H-13), 2.49−2.41 (m, 2H, H-15, H-13), 1.89 (d, ^4J = 1.0, 3H, H-18), 0.84 (d, ^3J = 6.9, H-20) ppm. ^{13}C NMR (100.7 MHz, $CDCl_3$): δ 148.4 (C_q, CO), 147.6 (C_q, Ph), 137.9 (C_q, C11), 128.7 (2CH, Ph), 128.1 (CH, Ph), 127.8 (2CH, Ph), 119.2 (C_q, C10), 93.1 (C_q, C14), 80.1 (CH, C12), 70.7 (CH_2, CH_2Ph), 69.9 (CH_2, C19), 46.5 (CH_2, C13), 35.4 (CH, C15), 14.1 (CH_3, C18), 10.2 (CH_3, C20) ppm. HRMS (ESI): m/z $[M + H]^+$ calcd for $[C_{17}H_{20}O_4Br]^+$ 367.0540, obsd 367.0541; calcd for $[C_{17}H_{20}O_4{}^{81}Br]^+$ 369.0519, obsd 369.0519. To confirm the configuration of **14a**, 1D-NOE spectra in MeOD were recorded (see Scheme 4).

Preparation of 2-Iodo-3-methyl-2-cyclopentenone (7b)[26]. A 3.40 mL portion of 3-methylcyclopentenone (**6**; 33.3 mmol, 1.00 equiv) was dissolved in 216 mL of freshly distilled DCM. At room temperature under argon 12.7 g of iodine (49.9 mmol, 1.50 equiv) and 3.8 g of pyridinium dichromate (10.0 mmol, 0.30 equiv) were added. The reaction mixture was stirred for 48 h at room temperature under argon until completeness. The mixture was filtered, and the precipitate was washed carefully with DCM. Subsequently, 1.00 M HCl was added to the filtrate, the layers were separated, and the organic layer was washed again with 1.00 M HCl, saturated $Na_2S_2O_3$ solution, and brine. After it was dried over $MgSO_4$, the organic layer was taken to dryness. The crude product was purified by flash chromatography over silica gel (cyclohexane/EtOAc 9/1 to 7/3); 6.10 g (27.4 mmol, 82%) of the desired product as a slightly yellow wax was obtained. R_f = 0.29 (cyclohexane/EtOAc 7/3). ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.75 (m, 2H, H-13), 2.58 (m, 2H, H-12), 2.22 (m, 3H, H-18) ppm. ^{13}C NMR (100.7 MHz, $CDCl_3$): δ 203.7 (C_q, C14), 179.8 (C_q, C11), 102.8 (C_q, C10), 34.4 (CH_2, C13), 33.3 (CH_2, C12), 22.2 (CH_3, C18) ppm. HRMS (EI): m/z $[M]^+$ calcd for $[C_6H_7OI]^+$ 221.9536, obsd 221.9533.

6-Iodo-7-methyl-1,4-dioxaspiro[4.4]non-6-ene (8b). To a solution of 2-iodo-3-methylcylopent-2-enone (1.00 g, 4.5 mmol, 1.00 equiv) in triethyl orthoformate (5.30 mL, 31.5 mmol, 7.00 equiv) were added ethylene glycol (1.80 mL, 31.5 mmol, 7.00 equiv) and *p*-toluenesulfonic acid (8.60 mg, 45.0 μmol, 0.01 equiv). The reaction mixture was stirred for 22 h at room temperature until conversion was complete (GC/MS), purged into 50.0 mL of 2.00 M NaOH solution, and extracted three times with EtOAc. The combined organic layers were washed with brine, dried over $MgSO_4$, and evaporated to dryness to yield the crude product as a black oil. Purification by column chromatography on alumina (pH 10, Brockmann activity 2) yielded 574 mg (2.16 mmol, 48%) of **8b** as a slightly yellow oil. R_f = 0.53 (cyclohexane/EtOAc 7/3). ^{1}H NMR (400 MHz, $CDCl_3$ filtered over basic Al_2O_3): δ 4.20 (m, 2H, CH_2-ketal), 3.98 (m, 2H, CH_2-ketal), 2.44 (m, 2H, H-12), 2.18 (m, 2H, H-13), 1.85 (t, ^4J = 0.9, 3H, H-18) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$ filtered over basic Al_2O_3): δ 151.4 (C_q, C11), 120.0 (C_q, C14), 98.2 (C_q, C10), 65.8 (CH_2-ketal), 34.6 (CH_2, C12/13), 34.6 (CH_2, C12/13, 19.8 (CH_3, C18) ppm. HRMS (EI): m/z $[M]^+$ calcd for $[C_8H_{11}O_2I]^+$ 265.9798, obsd 265.9790.

9-Iodo-8-methyl-1,4-dioxaspiro[4.4]non-8-en-7-one (9b). To a mixture of **8b** (574 mg, 2.16 mmol, 1.00 equiv), molecular sieves (4 Å), and 4.60 mL of a 34% solution of TBHP in $C_2H_4Cl_2$ (21.6 mmol, 10.0 equiv) was added $Cr(CO)_6$ (47.5 mg, 216 μmol, 0.10 equiv) under argon, and the reaction mixture was stirred at 40 °C for 22 h. At this time GC/MS analysis showed ca. 33% conversion. A solution of 1.00 mL of TBHP in $C_2H_4Cl_2$ (4.74 mmol, 2.20 equiv) was added, and the mixture was stirred for a further 46 h at 40 °C until all starting material had been consumed. The reaction mixture was filtered, water was added to the filtrate, and the mixture was extracted three times with EtOAc. The combined organic layers were washed with brine, dried over $MgSO_4$, and evaporated to dryness. The remaining yellow oil was dissolved in EtOAc and filtered several times over Celite. The filtrate was evaporated to dryness to yield 517 mg of a slightly yellow wax as the crude product **9b** (30.5 mmol, 58%). R_f = 0.46 (cyclohexane/EtOAc 9/1). IR (ATR): 2980 (w), 2900 (w), 1706 (vs), 1622 (m), 1472 (w) cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$, filtered over basic Al_2O_3): δ 4.30 (m, 2H, CH_2-ketal), 4.09 (m, 2H, CH_2-ketal), 2.78 (s, 2H, H-13), 1.87 (s, 3H, H-18) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 199.3 (C_q, C12), 151.7 (C_q, C11), 135.2 (C_q, C14), 111.3 (C_q, C10), 66.6 (2CH_2-ketal), 47.3 (CH_2, C13), 13.1 (CH_3, C18) ppm. HRMS (EI): m/z $[M]^+$ calcd for $[C_8H_9O_3I]^+$ 279.9591, obsd 279.9597.

(*S*)-9-Iodo-8-methyl-1,4-dioxaspiro[4.4]non-8-en-7-ol (10b). A mixture of (*R*)-2-methyl-CBS-oxazaborolidine solution in THF (185 μL, 1.00 M, 185 μmol, 0.10 equiv) and 4.0 mL of THF under argon in a flame-dried two-necked round-bottom flask was cooled to 0 °C, and dimethyl sulfide−borane (350 μL, 3.69 mmol, 2.00 equiv) was added dropwise. After the mixture was stirred for 30 min at 0 °C, a solution of **9b** (517 mg, 1.85 mmol, 1.00 equiv) in 4.00 mL of THF was added at 0 °C over a period of 3 h using a syringe pump and stirring was continued for 30 min at 0 °C. Methanol was added carefully at 0 °C, and the mixture was warmed to room temperature. Water was added, and the mixture was extracted three times with diethyl ether. The combined organic layers were washed with brine, dried over $MgSO_4$, and evaporated to dryness to yield 399 mg of crude **10b** as a pale yellow oil (77%, >98% ee determined by chiral GC). The crude product was used without further purification for the further syntheses. For analytical purposes 90.0 mg of the crude product was purified by column chromatography on silica gel which had been pretreated with NEt_3 (cyclohexane/EtOAc 9/1 to 7/3) to obtain 52.0 mg of the pure desired product as a colorless wax. R_f = 0.15 (cyclohexane/EtOAc 7/3). $[\alpha]^{20}_D$ = 5.27° (c = 0.64, $CHCl_3$ filtered over basic Al_2O_3). ^{1}H NMR (400 MHz, $CDCl_3$ filtered over basic Al_2O_3): δ 4.57 (s, br, 1H, H-12), 4.20 (m, 2H, CH_2-ketal), 3.99 (m, 2H, CH_2-ketal), 2.62 (dd, ^2J = 14.0, ^3J = 7.0, 1H, H-13), 2.02 (dd, ^2J = 13.9, ^3J = 3.7, 1H, H-13), 1.90 (dd, ^4J = 0.9, 3H, H-18) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$ filtered over basic Al_2O_3) δ 153.4 (C_q, C11), 116.4 (C_q, C14), 103.6 (C_q, C10), 75.6 (CH, C12), 66.2 (CH_2-ketal), 65.9 (CH_2-ketal), 45.4 (CH_2, C13), 16.72 (CH_3, C18) ppm. HRMS (EI): m/z $[M]^+$ calcd for $[C_8H_{11}O_3I]^+$ 281.9747, obsd 281.9748.

(*S*)-2-Iodo-4-(4-methoxybenzyloxy)-3-methylcyclopent-2-enone (5b). To a suspension of NaH (157 mg, 3.92 mmol, 2.00 equiv) in a flame-dried two-necked round-bottom flask in 10.0 mL of THF under argon was added dropwise a solution of crude **10b** (553 mg, 1.96 mmol, 1.00 equiv) in 10.0 mL of THF within 10 min at 0 °C. The reaction mixture was stirred for 30 min at room temperature, HMPA (1.40 mL, 7.84 mmol, 4.00 equiv) and *p*-methoxybenzyl bromide (583 μL, 3.92 mmol, 2.00 equiv) were added, and the mixture was stirred overnight at room temperature. After it was cooled with an ice bath, the mixture was carefully diluted with water and extracted three times with EtOAc. The combined organic layers were washed with brine, dried over $MgSO_4$, and evaporated to dryness to yield 1.35 g of crude (*S*)-8-(benzyloxy)-6-iodo-7-methyl-1,4-dioxaspiro-[4.4]non-6-ene as a yellow liquid. The crude product was used for the next reaction without further purification.

A solution of 1.35 g of crude (*S*)-8-(benzyloxy)-6-iodo-7-methyl-1,4-dioxaspiro[4.4]non-6-ene and a small amount of TosOH in 39.0 mL acetone/water (25/1) was stirred for 20 h under argon at room temperature (conversion was monitored by GC/MS). The reaction mixture was diluted with water and extracted three times with EtOAc. The combined organic layers were washed with brine, dried over $MgSO_4$, and evaporated to dryness. Purification by column chromatography on silica gel (cyclohexane/EtOAc 9/1) provided 205 mg of **5b** (573 μmol, 27% over four steps) as a yellow, viscous oil, R_f = 0.52 (cyclohexane/EtOAc 7/3). $[\alpha]^{20}_D$ = 39.4° (c = 0.85, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.27 (m, 2H, Ph), 6.90 (m, 2H, Ph), 4.63−4.55

(m, 2H, CH_2PhOMe, H-12), 4.49 (d, ^3J = 11.3, 1H, CH_2PhOMe), 3.82 (s, 3H, OCH_3), 2.81 (dd, ^2J = 18.1, ^3J = 5.9, 1H, H-13), 2.51 (dd, ^2J = 18.0, ^3J = 2.2, 1H, H-13), 2.22 (d, ^4J = 0.4, 3H, H-18) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 199.2 (C_q, C14), 177.7 (C_q, C11), 129.8 (2CH, PhOMe), 129.5 (C_q, Ph), 129.3 (C_q, Ph), 114.2 (2CH, Ph), 113.9 (C_q, C10), 79.0 (CH, C12), 71.9 (CH_2PhOMe), 55.5 (CH_3, OMe), 40.4 (CH_2, C13), 19.4 (CH_3, C18) ppm. HRMS (EI): m/z $[M]^+$ calcd for $[C_{14}H_{15}O_3I]^+$ 358.0060, obsd 358.0054.

(1*S*,4*S*)-2-Iodo-4-(4-methoxybenzyloxy)-3-methyl-1-(prop-1-en-2-yl)cyclopent-2-enol (12b). A water-free suspension of $CeCl_3$ in THF (4.10 mL, 0.10 g/mL, 1.66 mmol, 3.00 equiv; for the preparation, see ref 24) was added via a transfer cannula to a solution of **5b** (199 mg, 554 μmol, 1.00 equiv) in 8.80 mL of THF in a flame-dried Schlenk tube under positive argon pressure. The suspension was stirred for 3 h at room temperature, and a solution of isopropylmagensium bromide in THF (3.30 mL, 0.50 M, 1.66 mmol, 3.00 equiv) was added dropwise within 20 min. The reaction mixture was stirred at room temperature until all starting material was consumed (determined by GC/MS and by TLC control; 30 min). After it was cooled with an ice bath, the reaction mixture was carefully diluted with water and extracted three times with diethyl ether. The combined organic layers were washed with brine, dried over $MgSO_4$, and evaporated to dryness. Purification by column chromatography on silica gel (cyclohexane/EtOAc 9/1) yielded 193 mg (483 μmol, 87%, >87% de by NMR) of **12b** as a slightly yellow oil. R_f = 0.61 (cyclohexane/EtOAc 7/3). $[\alpha]^{20}_D$ = 13.0° (c = 0.05, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.27 (m, 2H, PhOMe), 6.89 (m, 2H, PhOMe), 5.14 (dd, ^4J = 0.7, 1.4, 1H, H-19), 4.97 (p, ^4J = 1.4, 1H, H-19), 4.51 (d, ^2J = 11.3, 1H, CH_2PhOMe), 4.44 (d, ^2J = 11.4, 1H, CH_2PhOMe), 4.35 (ddq, ^4J = 0.9, ^3J = 4.3, 7.2, 1H, H-12), 3.81, (s, 3H, OCH_3), 2.64 (dd, ^2J = 13.9, ^3J = 7.2, 1H, H-13), 2.20 (s, br, 1H, OH), 2.09 (dd, ^2J = 13.9, ^3J = 4.3, 1H, H-13), 1.89 (d, ^4J = 0.9, 3H, H-18), 1.57 (dd, ^4J = 0.7, 1.4, 3H, H-20) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 159.5 (C_q, PhOMe), 148.6 (C_q, C14), 146.6 (C_q, C11), 130.3 (C_q, PhOMe), 129.5 (2CH, PhOMe), 114.0 (C_q), 111.8 (2CH, PhOMe), 110.6 (C_q, C10), 87.4 (C_q, C15), 83.1 (CH, C12), 70.7 (CH_2PhOMe), 55.4 (CH_3, OMe), 43.2 (CH_2, C13), 18.6 (CH_3 C20), 17.2 (CH_3, C18) ppm. HRMS (ESI): m/z $[M]^+$ calcd for $[C_{17}H_{21}O_3INa]^+$ 423.0428, obsd 423.0425.

(1*S*,4*S*)-1-((*R*)-1-Hydroxypropan-2-yl)-2-iodo-4-(4-methoxybenzyloxy)-3-methylcyclopent-2-enol (13b). Freshly prepared (+)-$(Ipc)_2$BH (186 mg, 651 μmol, 1.50 equiv) was suspended in 2.10 mL of THF in a flame-dried Schlenk tube under positive argon pressure. At 0 °C a solution of **12b** (174 mg, 434 μmol, 1.00 equiv) in 1.50 mL of THF was added dropwise within 15 min. The reaction mixture was stirred for 60 min at room temperature, and since GC/MS monitoring revealed that the starting material had not been consumed completely, (+)-$(Ipc)_2$BH (124 mg, 434 μmol, 1.00 equiv) was added as a solid on cooling with an ice bath. The reaction mixture was stirred until conversion was complete (60 min) with warming to room temperature. At 0 °C aqueous NaOH (2.80 mL, 2.00 M, 5.69 mmol, 13.3 equiv) and an aqueous H_2O_2 solution (277 μL, 30%, 2.71 mmol, 6.30 equiv) were added dropwise to the reaction mixture, and the mixture was stirred for 3 h at room temperature. Water was added, the mixture was extracted three times with diethyl ether, and the combined organic layers were washed with brine, dried over $MgSO_4$, and evaporated to dryness at room temperature (*caution!* the product is very acid and temperature sensitive). After purification by column chromatography on deactivated silica gel (cyclohexane/EtOAc 7/3) 69.7 mg of **12b** was obtained as a slightly yellow oil (165 μmol, 38%). To calculate the diastereomeric excess, an analytical sample of the product was dissolved in *N*,*O*-bis(trimethylsilyl)acetamide and stirred at 80 °C for 30 min. Monitoring by GC/MS revealed a de of 80%. R_f = 0.07 (cyclohexane/EtOAc 7/3). $[\alpha]^{20}_D$ = 13.6° (c = 0.75, MeOH). ^{1}H NMR (400 MHz, MeOD): δ 7.28 (m, 2H, PhOMe), 6.89 (m, 2H, PhOMe), 4.50 (d, ^2J = 11.3, 1H, CH_2PhOMe), 4.43 (d, ^2J = 11.3, 1H, CH_2PhOMe), 4.27 (ddd, ^3J = 7.3, 4.8, ^4J = 1.0, 1H, H-12), 3.78 (s, 3H, OCH_3), 3.36 (dd, ^2J = 10.7, ^3J = 4.0, 1H, H-19), 3.03 (dd, ^2J = 10.7, ^3J = 8.3, 1H, H-19), 2.73 (dd, ^2J = 13.9, ^3J = 7.4, 1H, H-13), 1.99 (m, 1H, H-15), 1.83 (d, ^4J = 1.0, 3H, H-18), 1.73 (dd, ^4J = 13.8, ^3J = 4.7, 1H, H-13), 1.09 (d, ^3J = 6.8, 3H, H-20) ppm. ^{13}C NMR (100.6 MHz, MeOD): δ 178.1 (C_q), 148.0 (C_q, C11), 131.7 (C_q), 130.6 (2CH, PhOMe), 114.8 (2CH, PhOMe), 112.7 (C_q, C14), 86.4 (C_q, C10), 83.7 (CH, C12), 71.6 (CH_2PhOMe), 64.1 (CH_2, C19), 55.7 (CH_3, OMe), 44.0 (CH, C15), 41.1 (CH_2, C12), 17.1 (CH_3, C18), 11.6 (CH_3, C20) ppm. HRMS (ESI): m/z $[M]^+$ calcd for $[C_{17}H_{23}O_4INa]^+$ 441.0533, obsd 441.0525.

(1*S*,4*S*)-2-Iodo-4-(4-methoxybenzyloxy)-1-((*R*)-1-(4-methoxybenzyloxy)propan-2-yl)-3-methylcyclopent-2-enol (14b). In a flame-dried Schlenk tube NaH (5.80 mg, 60%, 145.5 μmol, 1.25 equiv) was suspended under positive argon pressure in 300 μL of THF. At 0 °C a solution of **13b** (48.7 mg, 116 μmol, 1.00 equiv) in 300 μL of THF was slowly added dropwise. The mixture was stirred for 20 min at 0 °C, HMPA (28.6 μL, 233 μmol, 2.00 equiv) and *p*-methoxybenzyl bromide (17.3 μL, 116 μmol, 1.00 equiv) were added, and stirring was continued for 1.5 h at 0 °C and for an additional 20 min at room temperature, after which the starting material was completely consumed. After the mixture was cooled with an ice bath, water was added, the aqueous phase was extracted three times with EtOAc, and the combined organic layers were washed with brine, dried over $MgSO_4$, and evaporated to dryness. Purification by column chromatography on silica yielded 29.4 mg of **14b** as a colorless oil (54.6 μmol, 47%, 80% de by NMR). R_f = 0.36 (cyclohexane/EtOAc 7/3). $[\alpha]^{20}_D$ = 3.87° (c = 0.31, MeOH). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.25−7.19 (m, 4H, PhOMe), 6.88−6.85 (m, 4H, PhOMe), 4.44 (dd, ^2J = 11.3, 9.8, 2H, CH_2PhOMe), 4.36 (d, ^2J = 11.4, 1H, CH_2PhOMe), 4.30 (d, ^2J = 11.4, 1H, CH_2PhOMe), 4.21 (ddd, ^3J = 7.0, 4.4, ^4J = 0.9, 1H, H-12), 3.80 (s, 6H, 2OCH_3), 3.46 (dd, ^2J = 9.5, ^3J = 5.8, 1H, H-19), 3.15 (dd, ^2J = 9.5, ^3J = 5.8, 1H, H-19), 2.86 (s, 1H, OH), 2.64 (dd, ^2J = 13.8, ^3J = 7.1, 1H, H-13), 2.18 (m, 1H, H-15), 1.88 (dd, ^2J = 13.8, ^3J = 4.4, 1H, H-13), 1.82 (d, ^4J = 0.8, 3H, H-18), 1.03 (d, ^3J = 6.9, 3H, H-20) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 159.4 (2C_q, PhOMe), 148.1 (C_q, C11), 130.5 (C_q), 130.3 (C_q), 129.5 (2CH, PhOMe), 129.5 (2CH, PhOMe), 114.0 (2CH, PhOMe), 113.9 (2CH, PhOMe), 110.3 (C_q, C10), 86.2 8 (C_q, C14), 82.4 (CH, C12), 73.0 (CH_2, CH_2PhOMe), 72.1 (CH_2, C19), 70.5 (CH_2, CH_2PhOMe), 55.4 (2CH_3, 2OMe), 41.9 (CH_2, C13), 41.5 (CH, C15), 17.3 (CH3, C18), 12.0 (CH_3, C20) ppm. HRMS (ESI): m/z $[M]^+$ calcd for $[C_{25}H_{31}O_5INa]^+$ 561.1108, obsd 561.1102.

(1*S*,4*S*)-2-Iodo-4-(4-methoxybenzyloxy)-1-((*R*)-1-(4-methoxybenzyloxy)propan-2-yl)-3-methylcyclopent-2-enyl Diethylcarbamate (3b). To a suspension of NaH (3.20 mg, 60%, 80 μmol, 2.00 equiv) in 300 μL of THF in a flame-dried flask was added dropwise a solution of **14b** (21.5 mg, 40 μmol, 1.00 equiv) in 300 μL of THF at room temperature, and the mixture was stirred for 30 min. 4-DMAP (4.90 mg, 40.0 μmol, 1.00 equiv) and diethylcarbamoyl chloride (52.2 μL, 399 μmol, 10.0 equiv) were added, and the reaction mixture was stirred overnight at 45 °C. After it was cooled to room temperature, the mixture was quenched by the addition of water and extracted three times with EtOAc. The combined organic layers were washed once with brine, dried over $MgSO_4$, and evaporated to dryness. Purification on deactivated silica gel (NEt_3, cyclohexane/EtOAc 9/1) yielded 6.3 mg of **3b** as a slightly yellow oil (9.90 μmol, 25%, >95% de by NMR). R_f = 0.41 (cyclohexane/EtOAc 7/3). $[\alpha]^{20}_D$ = 5.32° (c = 0.55, MeOH). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.26−7.18 (m, 4H, PhOMe), 6.86−6.84 (m, 4H, PhOMe), 4.50 (d, ^2J = 11.8, 1H, CH_2PhOMe), 4.42 (d, ^2J = 11.8, 1H, CH_2PhOMe), 4.35 (d, ^2J = 11.6, 1H, CH_2PhOMe), 4.30−4.26 (m, 2H, CH_2PhOMe, H-12), 3.80−3.80 (m, 6H, 2OCH_3), 3.34 - 3.12 (m, 6H, 2CH_2-carbamate, 2H-19), 2.77 (dd, ^2J = 13.3, ^3J = 7.3, 1H, H-13), 2.63 (dd, ^2J = 13.3, ^3J = 5.6, 1H, H-13), 2.53−2.49 (m, 1H, H-15), 1.84 (d, ^4J = 1.0, 3H, H-18), 1.13−1.10

(m, 6H, CH_3-carbamate), 1.08 (d, ^3J = 6.8, 3H, H-29). ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 159.2 ($2C_q$), 153.9 (C_q), 148.8 (C_q, C11), 130.6 ($2C_q$), 129.4 (2CH, PhOMe), 129.3 (2CH, PhOMe), 113.9 (4CH, PhOMe), 104.4 (C_q, C10), 92.3 (C_q, C14), 82.3 (CH, C12), 72.8 (CH_2, CH_2PhOMe), 70.9 (CH_2, C19), 69.7 (CH_2, CH_2PhOMe), 55.4 ($2CH_3$, 2OMe), 41.6 (CH_2, C13), 41.0 ($2CH_2$, CH_2-carbamate), 39.1 (CH, C15), 17.1 (CH_3, C18), 14.0 ($2CH_3$, CH_3-carbamate), 12.8 (CH_3, C20) ppm. HRMS (ESI): m/z $[M]^+$ calcd for $[C_{30}H_{40}O_6NINa]^+$ 660.1793, obsd 660.1789.

■ ASSOCIATED CONTENT

Supporting Information. Text, figures, and a table giving an explanation of the Mosher ester analysis, an exploration of different methods for the allylic oxidation of **8a**, and ^{1}H and ^{13}C spectra of all compounds synthesized. This material is available free of charge via the Internet at http://pubs.acs.org.

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■ REFERENCES

(1) Ballio, A.; Mauri, M.; Chain, E.; Deleo, P.; Tonolo, A.; Erlanger, B. *Nature* **1964**, *203*, 297.
(2) Aducci, P.; Marra, M.; Fogoliano, V.; Fullone, M. *J. Exp. Bot.* **1995**, *46*, 1463.
(3) Würtele, M.; Jelich-Ottmann, C.; Wittinghofer, A. *EMBO J.* **2003**, *22*, 987.
(4) Ottmann, C.; Marco, S.; Jaspert, N.; Marcon, C.; Schauer, N.; Weyand, M.; Vandermeeren, C.; Duby, G.; Boutry, M.; Wittinghofer, A.; Rigaud, J.-L.; Oecking, C. *Mol. Cell* **2007**, *25*, 427.
(5) Muslin, A.; Tanner, J.; Allen, P.; Shaw, A. *Cell* **1996**, *84*, 889.
(6) Hermeking, H. *Nat. Rev. Cancer* **2003**, *3*, 931.
(7) Rose, R.; Erdmann, S.; Bovens, S.; Wolf, A.; Rose, M.; Hennig, S.; Waldmann, H.; Ottmann, C. *Angew. Chem., Int. Ed.* **2010**, *49*, 4129.
(8) de Vries-van Leeuwen, I. J.; Kortekaas-Thijssen, C.; Mandouckou, J. A. N.; Kas, S.; Evidente, A.; de Boer, A. H. *Cancer Lett.* **2010**, *293*, 198.
(9) Asahi, K.; Honma, Y.; Hazeki, K.; Sassa, T.; Kubohara, Y.; Sakurai, A.; Takahashi, N. *Biochem. Biophys. Res. Commun.* **1997**, *238*, 758.
(10) Honma, Y.; Ishii, Y.; Sassa, T.; Asahi, K.-I. *Leukemia Res.* **2003**, *27*, 1019.
(11) Kasukabe, T.; Okabe-Kado, J.; Kato, N.; Sassa, T.; Honma, Y. *Breast Cancer Res.* **2005**, *7*, 1097.
(12) Kato, N.; Okamoto, H.; Takeshita, H. *Tetrahedron* **1996**, *52*, 3921.
(13) Li, F.; Kato, N.; Mori, A.; Takeshita, H.; Sassa, T. *Chem. Lett.* **1997**, *12*, 1207.
(14) Kato, N.; Kataoka, H.; Ohnuchi, S.; Tanaka, S.; Takeshita, H. *J. Chem. Soc., Chem. Commun.* **1988**, *5*, 354.
(15) Song, D.; McDonald, R.; West, F. *Org. Lett.* **2006**, *8*, 4075.
(16) Molander, G.; Harris, C. *J. Am. Chem. Soc.* **1995**, *117*, 3705.
(17) Williams, D. R.; Robinson, L. A.; Nevill, C. R.; Reddy, J. P. *Angew. Chem., Int. Ed.* **2007**, *46*, 915.
(18) Paquette, L.; Sun, L.; Friedrich, D.; Savage, P. *J. Am. Chem. Soc.* **1997**, *119*, 8438.
(19) Molander, G.; McKie, J. *J. Org. Chem.* **1995**, *60*, 872.
(20) Molander, G.; McKie, J. *J. Org. Chem.* **1994**, *59*, 3186.
(21) Cram, D.; Elhafez, F. *J. Am. Chem. Soc.* **1952**, *74*, 5828.
(22) Mengel, A.; Reiser, O. *Chem. Rev.* **1999**, *99*, 1191.
(23) Berkessel, A.; Menche, D.; Sklorz, C.; Schröder, M.; Paterson, I. *Angew. Chem., Int. Ed.* **2003**, *42*, 1032.
(24) Imamoto, T.; Takiyama, N.; Nakamura, K.; Hatajima, T.; Kamiya, Y. *J. Am. Chem. Soc.* **1989**, *111*, 4392.
(25) Won, Y.; Joung, U.; Kwon, H.; Lee, B. *J. Organomet. Chem.* **2003**, *677*, 133.
(26) Johnson, C.; Adams, J.; Braun, M.; Senanayake, C.; Wovkulich, P.; Uskokovic, M. *Tetrahedron Lett.* **1992**, *33*, 917.
(27) Bovonsombat, P.; Angam, G.; Edward Mc, N. *Tetrahedron Lett.* **1994**, *35*, 6787.
(28) Janessen, C.; Simons, L.; Godefroi, E. *Synthesis* **1982**, 389.
(29) Sharples, K.; Lauer, R. *J. Am. Chem. Soc.* **1972**, *94*, 7154.
(30) Pearson, A.; Chen, Y.; Han, G.; Hsu, S.; Ray, T. *J. Chem. Soc., Perkin Trans. 1* **1985**, 267.
(31) Corey, E.; Helal, C. *Angew. Chem., Int. Ed.* **1998**, *37*, 1987.
(32) Hoye, T. R.; Jeffrey, C. S.; Shao, F. *Nat. Protoc.* **2007**, *2*, 2451.
(33) Stern, A.; Rohde, J.; Swenton, J. *J. Org. Chem.* **1989**, *54*, 4413.
(34) Wang, Q.; Chen, C. *Org. Lett.* **2008**, *10*, 1223.
(35) Brown, H.; Ramachandran, P. *J. Organomet. Chem.* **1995**, *500*, 1.