Formal Synthesis of (−)-Cephalotaxine

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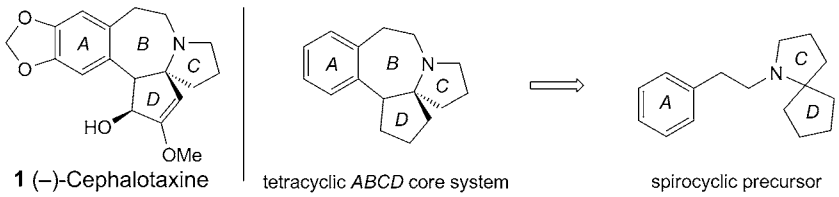
Dedicated with great admiration to Prof. *Dieter Seebach* on the occasion of his 75th birthday

A formal synthesis of (−)-cephalotaxine (**1**) by means of a highly stereoselective radical carboazidation process is reported. The synthesis begins with the protected (*S*)-cyclopent-2-en-1-ol derivative **10** and uses the concept of self-reproduction of a stereogenic center (*Schemes 5* and *6*). For this purpose, the double bond adjacent to the initial chiral center in **10** is converted into an acetonide after stereoselective dihydroxylation. The initial alcohol function is used to build an exocyclic methylene group suitable for the carboazidation process **8** → **7** (Scheme 7). Finally the protected diol moiety is converted back to an alkene (**14** → **15** → **6**) and used for the formation of ring *B via* a *Heck* reaction (**6** → (−)-**16**; *Scheme 8*).

Introduction. – (−)-Cephalotaxine (**1**) is the parent structure of the *Cephalotaxus* alkaloids, a unique class of benzazepine alkaloids [1]. Its original pentacyclic structure and the clinically established therapeutic potential of its ester derivatives (*i.e.*, harringtonine and homoharringtonine) as antileukemia agents make it a popular target for synthesis as illustrated by the early work of *Auerbach* and *Weinreb* [2] and *Semmelhack* and co-workers [3]. Several strategies for the construction of the *ABCD* ring system have been developed. One of the most common strategy, pioneered by *Semmelhack* and co-workers, consists of forming the *B*-ring by starting from a spirocyclic precursor containing the *ACD* rings (*Scheme 1*) [3]. Several different cyclization procedures leading to ring *B* involving radical cyclization [4], ketone arylation [3][5], *Friedel–Crafts* alkylation [6], intramolecular *Heck* reactions [7], intramolecular *Schmidt* reaction [8], and transannular conjugate addition [9] have been reported.

Scheme 1. *(−)-Cephalotaxine* (**1**) *and the* B-*Ring-Closing Synthetic Strategy*



The synthesis of the key spirocyclic intermediates containing the rings *ACD* in optically pure form is of primary importance for the efficacy of the whole synthesis, and

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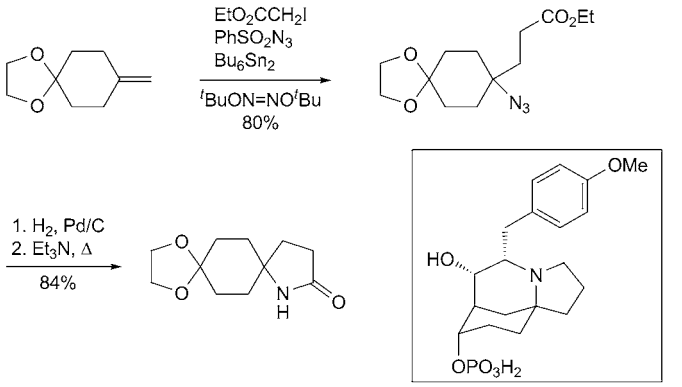
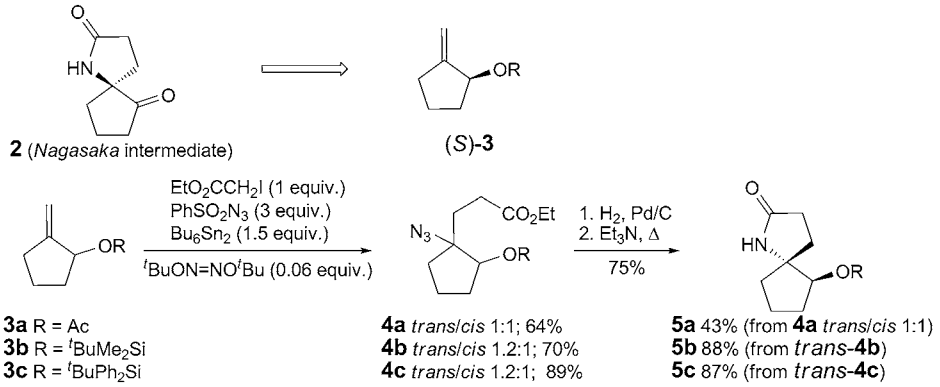
improvement of this part of the synthesis is still strongly desired. Recently, we have reported a radical carboazidation procedure very well suited for the preparation of secondary and tertiary C-atom centers substituted by an amino group [10]. This process was the key step of our recent synthesis of lepadiformines [11], cylindricine C [12], hyacinthacine A_1 [13], and indolizidines [14]. The preparation of the spirocyclic systems such as the core of (±)-des(methylamino)-FR901483 *via* carboazidation of a methylenecycloalkane derivative followed by reductive lactamization was reported (*Scheme 2*) [10c]. Here, we extend this approach to the synthesis of optically pure (−)-cephalotaxine (**1**). A method allowing an efficient control of the configuration of the amino-substituted spiro center was developed.

Scheme 2. *Preparation of the Spirocyclic Core of (±)-Des(methylamino)-FR901483* [10c]



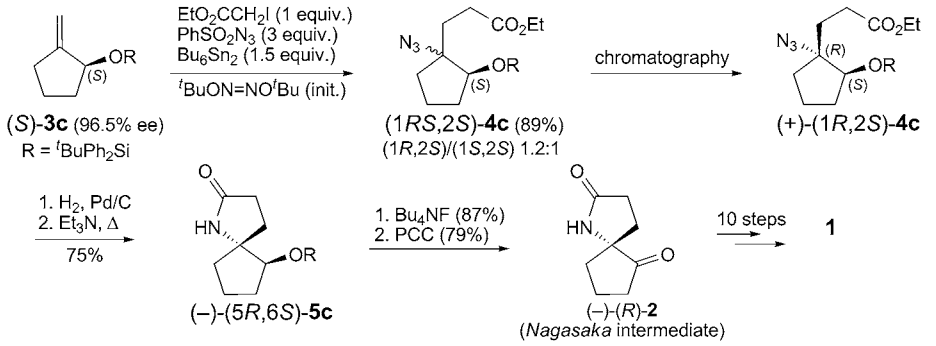
***Nagasaka*'s Intermediate 2 from 2-Methylenecyclopentanol (3; R = H).** – The spirocyclic amide **2**, an intermediate in *Nagasaka* and co-workers' synthesis of cephalotaxine [15], was selected as target for our approach. Compound **2** has been prepared with moderate diastereoselectivities by *Royer* and co-workers. [16] and was expected to be readily prepared from protected (1*S*)-2-methylenecyclopentanol derivative (*S*)-**3** according to *Scheme 3*. The stereochemical outcome of the key carboazidation step was examined first on protected methylenecyclopentanol derivatives. Racemic 2-methylenecyclopentanol was protected as an acetate ester **3a**, a (*tert*-butyl)dimethylsilyl ether **3b**, and a (*tert*-butyl)diphenylsilyl ether **3c**. The carboazidation of the protected allylic alcohols **3a**–**3c** afforded the expected azido derivatives **4a**–**4c** in 63–88% yield. However, the level of stereoselectivity did not exceed a *trans*/*cis* 1.2:1 ratio even with the large (*tert*-butyl)diphenylsilyl protecting group [17]. A 1:1 diastereoisomer mixture **4a** was reduced with H_2 over Pd/C to the amine that underwent lactamization upon heating in the presence of triethylamine to afford **5a** as a single *trans*-isomer. The *cis*-isomer was isolated as a noncyclized amino ester. Under similar conditions, *trans*-**4b** and *trans*-**4c** afforded the spirolactams **5b** and **5c** in 75% and 87% yield, respectively.

Scheme 3. *Retrosynthesis of* Nagasaka *Intermediate* **2** *and Configuration of the Carboazidation Step*



The silylated (1*S*)-2-methylenecyclopentanol derivative (*S*)-**3c** (96.5% ee) was prepared from racemic cyclopentanol *via* enzymatic enantioselective acetylation with hog-pancreas lipase (PPL) according to the procedure developed by *Burgess* and *Jennings* for allylic alcohols [18]. Carboazidation of (*S*)-**3c** afforded, as expected from the racemic series, azido derivative **4c** in 89% yield as a 1.2:1 mixture of isomers (*Scheme 4*). After separation by flash chromatography[1]), the major azido ester (+)-(1*R*,2*S*)-**4c** was converted into the spirolactam (−)-(5*R*,6*S*)-**5c** by reductive lactamization. Desilylation with Bu_4NF and oxidation of the free alcohol with pyridinium chlorochromate (PCC) of the free alcohol afforded *Nagasaka* intermediate (−)-(*R*)-**2**. Conversion of this intermediate into (−)-cephalotaxine (**1**) according to *Kuehne*'s procedure [6b] has been reported by *Nagasaka* and co-workers [15] and requires 10 steps.

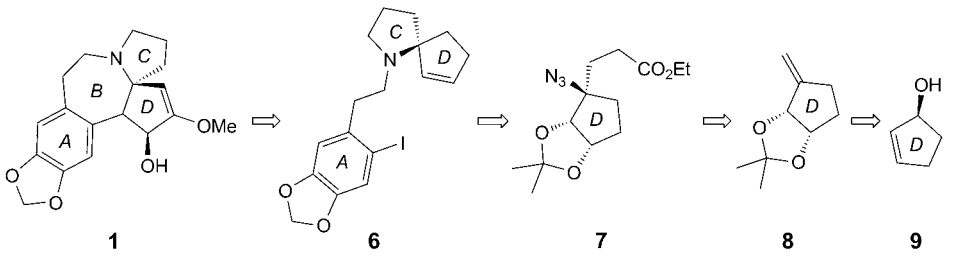
Scheme 4. *Synthesis of Optically Pure* Nagasaka *Intermediate (−)-(*R*)-***2***



[1]) When the flash chromatography was run with AcOEt/hexane as eluent, the minor diastereoisomer decomposed on the column, and only the *trans*-isomer (+)-(1*R*,2*S*)-**4c** was isolated in 59% yield from (*S*)-**3c**.

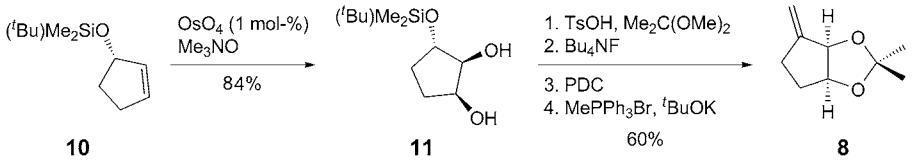
***Mori*'s Intermediate (−)-16 from (1*S*)-Cyclopent-2-en-1-ol (9).** – Since the first approach leading to *Nagasaka*'s intermediate did not allow an efficient control of the configuration of the spiro center, another approach starting from (1*S*)-cyclopent-2-en-1-ol (**9**) [19] was developed. The key disconnections are depicted in *Scheme 5*. Formation of the *B* ring will be performed from **6** *via* a *Heck* intramolecular cross-coupling reaction according to the work of *Tietze* and *Schirok* [7a][7b] and *Yoshida* and co-workers [7d]. The C=C bond necessary for the *Heck* cross-coupling process corresponds to the one of cyclopentenol **9**. Remarkably, this C=C bond was used to control the configuration of the carboazidation step by temporary formation of an acetonide protected diol in compounds **7** and **8**. A high level of stereoselectivity is expected for the carboazidation step due to the bicyclic nature of alkene **8**. Thus, the stereogenic center of cyclopentenol **9** will be used to control the configuration of the diol, then be destroyed when the methylenecyclopentane derivative **8** is built, and finally by formed again during the carboazidation step leading to **7**. This strategy corresponds to the self-regeneration of stereogenic centers (SRS), a general concept of asymmetric synthesis developed by *Seebach* and co-workers [20].

Scheme 5. *Key Disconnections for a Stereoselective Synthesis of (−)-Cephalotaxine* (**1**) *by Means of the SRS Concept*



The synthesis of the methylenecyclopentane derivative **8** started with the silyl ether **10**, easily prepared on large scale in 96% ee according to our recently published procedure [19] (*Scheme 6*). Dihydroxylation of the C=C bond of **10** with OsO_4 afforded diol **11** as a single diastereoisomer that was protected as an acetonide. Desilylation with Bu_4NF fluoride, oxidation of the alcohol to the corresponding ketone with pyridinium dichromate (PDC), and finally *Wittig*-type methylenation afforded the bicyclic alkene **8**.

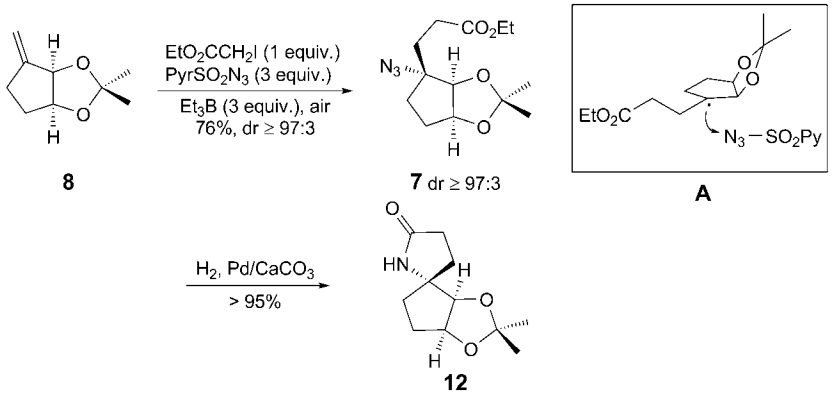
Scheme 6. *Preparation of the Methylenecyclopentane* **8**



The carboazidation of **8** was run under tin-free conditions with ethyl iodoacetate and pyridine-3-sulfonyl azide by using triethylborane and air to initiate the radical process (*Scheme 7*) [21]. As anticipated, the azido ester **7** was obtained with a very high

diastereoselectivity (dr ≥ 97:3). This high stereoselectivity resulted from an *exo*-selective azidation of the bicyclic radical according to model **A** (*Scheme 7*). Reduction of the azide with H_2 and $Pd/CaCO_3$ as a catalyst afforded directly the desired spirolactam **12**. The whole sequence depicted in *Schemes 6* and *7* allowed to convert the protected allyl alcohol **10** into the spirolactam **12** in 7 steps and ≥35% yield with excellent control of the configuration.

Scheme 7. *Preparation of the Key Lactam* **12** via *Highly Stereoselective Carboazidation*

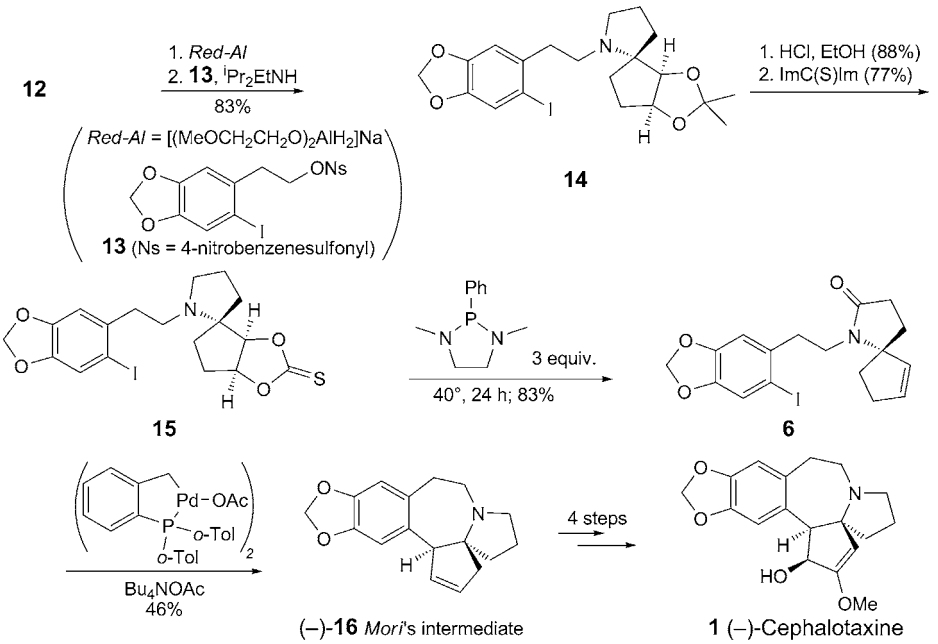


For the conversion of **12** to (−)-cephalotaxine (**1**), spirolactam **12** was first reduced with *Red-Al*® to the corresponding spirocyclic amine (*Scheme 8*). The crude amine was *N*-alkylated with nosylate **13** to afford **14** in 83% yield from **12**. After hydrolysis of the acetonide, several procedures were examined for the direct conversion of the diol to the alkene but none of them was successful. Finally, conversion of the diol to the thiocarbonate **15** with 1,1′-(thiocarbonyl)bis[1*H*-imidazole] followed by treatment with 1,3-dimethyl-2-phenyl-1,3,2-diazaphospholidine (*Corey–Hopkins* reagent) [22] afforded the desired alkene **6** in 80% yield. As anticipated and in contrast to the approach developed by *Hayes* and co-workers [6j], no racemization took place during the synthesis of **6**. Optically active **6** has been recently prepared by *Zhao* and *Mariano* [23], but the key *Heck* cyclization has only been reported for racemic **6** by *Yoshida* and co-workers [7d]. Formation of ring *B via Heck* intramolecular reaction according to *Tietze* and *Schirok*'s procedure [7a][7b] with *Hermann* and co-workers' catalyst [24] afforded (−)-**16** in 46% yield[2]), an advanced intermediate for the synthesis of (−)-cephalotaxine (**1**). The physical and spectroscopic properties of **1** matches the one reported by *Mori*, *Tietze*, *Hayes*, and their co-workers [6d][6j][7a][7b]. Conversion of **16** to (−)-cephalotaxine (**1**) in 4 steps has been described by *Isono* and *Mori* [6d].

Conclusions. – We developed a formal synthesis of (−)-cephalotaxine (**1**) based on a radical carboazidation process. The starting material was (1*S*)-cyclopent-2-en-1-ol, a chiral building block easily available on a large scale. Remarkably, all chemical

[2]) *Tietze* and *Schirok* reported the cyclization of the corresponding aryl bromide to **16** in 81% yield [7a][7b]. *Yoshida* and co-workers obtained **16** from iodide **6** in 60% yield [7d]. In our case, no attempt to optimize the cyclization was undertaken.

Scheme 8. *Cephalotaxine Synthesis, Formation of Ring* B



transformations occured with excellent stereoselectivity. The stereogenic center of (1*S*)-cyclopent-2-en-1-ol was used to control all the asymmetric centers of the target molecules. For this purpose, it was destroyed and rebuilt as a quaternary amino-subtituted C-atom center following the concept of self-regeneration of stereogenic centers.

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Experimental Part

1. *General.* All reactions were performed under N_2, heat-gun dried glassware were used, and standard precautions against moisture were taken. Commercial reagents were used as received. Solvents for reactions (distilled THF, Et_2O, benzene, toluene, and CH_2Cl_2) were purified and dried by filtration through columns of dried alumina under a positive pressure of Ar. Solvents for extraction and flash column chromatography were of technical grade and were distillated prior to use. TLC: SiO_2 *60* F_{254} plates. Flash column chromatography (FC): Silica gel *60* (SiO_2; 40–60 μm). GC: *CE-Instruments* HR-GC, series *8532*; *Macherey-Nagel Optima δ-3* column i.d. 0.25 mm, 30 m. M.p.: *Büchi-B-545* apparatus; uncorrected. IR Spectra: *Jasco-FT-IR-460-Plus* spectrometer, equipped with a *Specac-MKII-Golden-Gate* single-reflection diamond ATR system; $\tilde{\nu}$ in cm^{-1}. ^1H- and ^{13}C-NMR Spectra: *Bruker-Avance-300* spectrometer, at 300 (^1H) and 75 MHz (^{13}C), or *Bruker-Avance-II-400* spectrometer, at 400 (^1H) and 100 MHz (^{13}C); at 22° unless otherwise stated, δ in ppm rel. to $CHCl_3$ as internal standard (δ(H) 7.26 and δ(C) 77.0), *J* in Hz. Low and high-resolution MS: *Waters-Micromass-Autospec-Q* spectrometer in the EI mode at 70 eV; in *m*/*z* (rel. %). GC/MS: *Finnigan-Trace-GC-2000* gas chromatograph equipped with an autosampler and a *Finnigan-Trace-MS* mass-selective detector.

2. *General Procedure A.* To a stirred soln. of a methylenecyclopentane derivative (1.0 mmol) in dry benzene (2.0 ml) were added $PhSO_2N_3$ (550 mg, 3.0 mmol), ethyl iodoacetate (124 mg, 0.12 ml, 1.0 mmol), Bu_6Sn_2 (870 mg, 0.76 ml, 1.5 mmol), and ^{t}BuON=NO^{t}Bu (6 mg, 0.03 mmol). The resulting mixture was heated under reflux and N_2. After 2 h, a second portion of ^{t}BuON=NO^{t}Bu (6 mg, 0.03 mmol) was added, and the mixture was further heated under reflux for 2 h. The solvent was evaporated and the crude product filtered through SiO_2. Elution with hexane allowed to remove tin residues, and a mixture of hexane/AcOEt 9:1 afforded a crude product that was further purified by FC (hexane/AcOEt).

Caution: Since organic azides are capable of exploding, *it is strongly recommended to apply standard safety rules and to use a safety shield*.

3. *General Procedure B.* To a stirred soln. of azido derivative (1.0 mmol) in dry EtOH (4.0 ml) was added 10% Pd/C (30 wt.-%). The mixture was stirred under H_2 (30 bar) for 36 h. The slurry was filtered through *Celite*®, and the resulting soln. was treated with Et_3N (5.0 mmol, 0.70 ml) and heated under reflux for 4 h. Then the solvent was evaporated and the residue purified by FC (AcOEt/MeOH).

4. *Synthesis of the* Nagasaka *Intermediate* **2**. *2-Methylenecyclopentyl Acetate* (**3a**). Acetic anhydride (10 ml, 106 mmol) and pyridine (2 ml, 24 mmol) were added to 2-methylenecyclopentanol [25] (0.98g, 10 mmol). After stirring for 18 h at r.t., 1N aq. $NaHCO_3$ was added slowly. The resulting mixture was extracted with AcOEt (3 × 50 ml), the combined org. phase washed with dil. HCl soln. (3 × 30 ml) and brine (2 × 50 ml), dried (Na_2SO_4), and concentrated, and the residue purified by FC (hexane/AcOEt 95:5): **3a** (1.24 g, 89%). Colorless oil. Physical and spectral data: in accordance with [26].

*(*tert*-Butyl)dimethyl[(2-methylenecyclopentyl)oxy]silane* (*=1-{[1,1-Dimethylethyl)dimethylsilyl]-2-methylenecyclopentane*; **3b**). To a soln. of 2-methylenecyclopentanol (672 mg, 7 mmol) and 2,6-lutidine (=2,6-dimethylpyridine; 0.89 ml, 7.7 mmol) in CH_2Cl_2 (10 ml) at 0° was added dropwise ^{t}BuMe$_2$SiO-SO_2CT_3 (1.77 ml, 7.7 mmol). The mixture was stirred at 0° for 2 h, and the reaction was stopped by adding 20 ml of sat. aq. NH_4Cl soln. The aq. phase was extracted with CH_2Cl_2 (3 × 20 ml), the combined org. phase washed with brine (20 ml), dried (Na_2SO_4), and concentrated, and the residue purified by FC (hexane/AcOEt 98.5:1.5): **3b** (1.08 g, 73%). Colorless oil. R_f (hexane/AcOEt 98:2) 0.26. IR (film): 3080, 2955, 1664, 835. ^{1}H-NMR (300 MHz, $CDCl_3$): 5.05–5.02 (*m*, 1 H); 4.95–4.92 (*m*, 1 H); 4.42–4.38 (*m*, 1 H); 2.48–2.26 (*m*, 2 H); 1.98–1.88 (*m*, 1 H); 1.84–1.71 (*m*, 1 H); 1.62–1.43 (*m*, 2 H); 0.93 (*s*, 9 H); 0.11 (*s*, 3 H); 0.09 (*s*, 3 H). ^{13}C-NMR (75 MHz, $CDCl_3$): 154.1; 106.2; 75.5; 35.4; 29.3; 25.9; 20.7; −4.6; −4.7. HR-EI-MS: 212.1595 ($C_{12}H_{24}OSi^+$; calc. 212.1596). Physical and spectral data: in accordance with [27].

*(*tert*-Butyl)[(2-methylenecyclopentyl)oxy]diphenylsilane* (*={[(1,1-Dimethylethyl)diphenylsilyl]-oxy}-2-methylenecyclopentane*; **3c**). To a stirred soln. of 2-methylenecyclopentanol (1.31 g, 13.3 mmol) and 1*H*-imidazole (2.00 g, 29.3 mmol) in DMF (15 ml) at r.t. was added ^{t}BuPh$_2$Si (5.6 ml, 14.7 mmol). The mixture was stirred for 5 h at r.t. Then the soln. was diluted with CH_2Cl_2 (50 ml), washed with 1N $NaHSO_4$ (2 × 50 ml), H_2O (2 × 50 ml), and brine (50 ml), dried (Na_2SO_4), and concentrated *in vacuo*. The residue was purified by FC (hexane/AcOEt 99:1): **3c** (3.88 g, 87%). R_f (hexane/AcOEt 9:1) 0.77. IR (film): 3446, 2957, 1728, 1112. ^{1}H-NMR (300 MHz, $CDCl_3$): 7.75–7.69 (*m*, 4 H), 7.48–7.38 (*m*, 6 H); 5.09–5.06 (*m*, 1 H); 4.48–4.43 (*m*, 1 H); 2.49–2.36 (*m*, 1 H); 2.31–2.19 (*m*, 1 H); 1.82–1.72 (*m*, 1 H); 1.70–1.39 (*m*, 3 H); 1.12 (*s*, 9 H). ^{13}C-NMR (75 MHz, $CDCl_3$): 153.8; 135.9; 135.8; 129.6; 127.5; 127.5; 106.7; 76.2; 35.2; 29.2; 27.0; 20.7. HR-EI-MS: 336.1909 ($C_{22}H_{28}OSi^+$; calc. 336.1909).

*(+)-(*tert*-Butyl)[(2-methylenecyclopentyl)oxy]diphenylsilane* ((*S*)-**3c**) *and (+)-2-Methylenecyclopentyl Acetate* ((+)-**3a**). Hog-pancreas lipase (PPL; 2.0 g), vinyl acetate (14.7 ml, 160 mmol)), and 2-methylenecyclopentanol (3.92 g, 40 mmol) were added to ground, activated 4-Å molecular sieves (5 g) in hexane (350 ml) [18]. The mixture was stirred at 25° and the reaction was followed by GC. After 8 h (51% conversion by CC), the soln. was filtered and the filtrate concentrated. The crude mixture of alcohol and acetate (4.5 g) was dissolved in DMF (15 ml) and treated with ^{t}BuPh$_2$SiCl (5.55 g, 5.17 ml) and 1*H*-imidazole (2.75 g) and stirred for 6 h at r.t. The soln. was diluted with CH_2Cl_2 (100 ml), the org. phase washed with 1M $NaHSO_4$ (2 × 30 ml) and brine (30 ml), dried (Na_2SO_4), and concentrated, and the crude product purified by FC (cyclohexane/^{t}BuOMe 95:5): (*S*)-**3c** (4.07 g, 33%) and (+)-**3a** (2.00 g, 39%). (*S*)-**3c**: $[\alpha]_D^{25} = +13$ ($c = 0.9$, $CHCl_3$). The optical purity and the abs. configuration were determined after desilylation of (*S*)-**3c** to (+)-(1*S*)-2-methylenecyclopentanol [28].

Ethyl 2-(Acetyloxy)-1-azidocyclopentanepropanoate (**4a**). According to the *General Procedure A*, from alkene derivative **3a** (420 mg, 3.0 mmol), ethyl iodoacetate (642 mg, 0.35 ml 3.0 mmol), $PhSO_2N_3$ (1.65 g, 9.0 mmol), Bu_6Sn_2 (2.27 ml, 4.5 mmol), and ^{t}BuON=NO^{t}Bu (35 mg, 0.18 mmol). The crude product was purified by FC (hexane/AcOEt 93:7): **4a** (518 mg, 64%; 1:1 diastereoisomer mixture). Colorless oil . R_f (hexane/AcOEt 9:1) 0.2. IR (film): 2981, 2108 (N_3), 1738, 1236. ^{1}H-NMR (300 MHz, $CDCl_3$): 4.93–4.88 (*m*, 1 H); 4.15–4.08 (*m*, 2 H); 2.49–2.30 (*m*, 2 H); 2.25–1.98 (*m*, 6 H); 1.88–1.56 (*m*, 6 H); 1.26–1.22 (*m*, 3 H). ^{13}C-NMR (75 MHz, $CDCl_3$): 173.0; 172.8; 170.3; 169.8; 80.1; 78.7; 73.7; 70.7; 60.6; 60.5; 33.2; 32.2; 30.6; 30.5; 29.6; 29.5; 28.6; 28.1; 21.1; 20.8; 20.5; 18.9; 14.1. HR-ESI-MS: 292.1263 ($C_{12}H_{19}N_3NaO_4^+$; calc. 292.1273).

*Ethyl 1-Azido-2-{[(*tert*-butyl)dimethylsilyl]oxy}cyclopentanepropanoate* (**4b**). According to the *General Procedure A*, from alkene derivative **3b** (637 mg, 3.0 mmol), ethyl iodoacetate (642 mg, 0.35 ml 3.0 mmol), $PhSO_2N_3$ (1.65 g, 9.0 mmol), Bu_6Sn_2 (2.27 ml, 4.5 mmol), and ^{t}BuON=NO^{t}Bu (35 mg, 0.18 mmol). Purification by FC (hexane/AcOEt 98.5:1.5) gave **4b** (717 mg, 70%) as a 1.2:1 mixture of diastereoisomers. Further purification by FC (hexane/AcOEt 98.5:1.5) allowed the isolation of the major *trans*-**4b** as a single diastereoisomer.

trans-**4b**: Colorless oil. R_f (hexane/AcOEt 9:1) 0.52. IR (film) 2105 (N_3), 1729. ^{1}H-NMR (300 MHz, $CDCl_3$): 4.14 (*q*, *J* = 7.4, 2 H); 3.87 (*dd*, *J* = 5.1, 2.8, 1 H). 2.43–2.38 (*m*, 2 H); 2.11–1.92 (*m*, 3 H); 1.84–1.55 (*m*, 5 H); 1.25 (*t*, *J* = 7.4, 3 H); 0.87 (*s*, 9 H); 0.07 (*s*, 3 H); 0.06 (*s*, 3 H). ^{13}C-NMR (75 MHz, $CDCl_3$): 173.4; 78.1; 75.0; 60.4; 32.9; 32.2; 29.9; 28.2; 25.7; 20.2; 17.9; 14.2; −4.3; −5.1. HR-ESI-MS: 364.2016 ($C_{16}H_{31}N_3NaO_3Si^+$; calc. 364.2032).

*Ethyl 1-Azido-2-{[(*tert*-butyl)diphenylsilyl]oxy}cyclopentanepropanoate* (**4c**). According to the *General Procedure A*, from alkene derivative **3c** (1.01 g, 3.0 mmol), ethyl iodoacetate (642 mg, 0.35 ml 3.0 mmol), $PhSO_2N_3$ (1.65 g, 9.0 mmol), Bu_6Sn_2 (2.27 ml, 4.5 mmol), and ^{t}BuON=NO^{t}Bu (35 mg, 0.18 mmol). Purification by FC (hexane/AcOEt 98.8:1.2) gave **4c** (1.24 g, 89%) as a 1.2:1 mixture of diastereoisomers. Further purification by FC (hexane/AcOEt 98.5:1.5) enabled to isolate the major *trans*-**4c** (0.82 g, 59%). The minor decomposed slowly during FC and could not be isolated. *trans*-**4c**: Colorless oil. R_f (hexane/AcOEt 9:1) 0.39. IR (film): 2104 (N_3), 1735. ^{1}H-NMR (300 MHz, $CDCl_3$): 7.69–7.62 (*m*, 4 H); 7.48–7.35 (*m*, 6 H); 4.15 (*q*, *J* = 7.0, 2 H); 3.97–3.94 (*m*, 1 H); 2.42–2.39 (*m*, 2 H); 2.23–2.05 (*m*, 2 H); 1.93–1.51 (*m*, 6 H); 1.27 (*t*, *J* = 7.0, 3 H); 1.07 (*s*, 9 H). ^{13}C-NMR (75 MHz, $CDCl_3$): 173.2; 135.8; 135.7; 134.2; 132.9; 129.8; 129.7; 127.7; 127.5; 79.2; 75.0; 60.4; 32.2; 32.1; 29.8; 28.2; 26.9; 20.0; 19.2; 14.2. HR-ESI-MS: 488.2347 ($C_{26}H_{35}N_3NaO_3Si^+$; calc. 488.2345).

*(+)-(1*R*,2*S*)-Ethyl 1-Azido-2-{[(*tert*-butyl)diphenylsilyl]oxy}cyclopentanepropanoate* ((+)-(1*R*,2*S*)-**4c**). According to the procedure described for racemic **4c**, from (*S*)-**3c** (1.01 g, 3.0 mmol). $[\alpha]_D^{25} = +18$ (*c* = 1.0, $CHCl_3$).

2-Oxo-1-azaspiro[4.4]non-6-yl Acetate (=*6-(Acetyloxy)-1-azaspiro[4.4]nonan-2-one*; **5a**). According to the *General Procedure B*, from **4a** (269 mg, 1.0 mmol) and 10% Pd/C (80 mg). Purification by FC (AcOEt) gave **5a** (85 mg, 43%, one diastereoisomer) together with the uncyclized amino ester (22 mg).

Data of **5a**: White solid. M.p. 120–123°. R_f (AcOEt/MeOH 99:1) 0.4. IR ($CHCl_3$): 3423, 3019, 1731, 1690. ^{1}H-NMR (300 MHz, $CDCl_3$): 7.02 (br. *s*, 1 H); 4.90 (*dd*, *J* = 7.0, 5.7, 1 H); 2.46–2.24 (*m*, 3 H); 2.21–2.03 (*m*, 1 H); 2.05 (*s*, 3 H); 1.87–1.58 (*m*, 6 H). ^{13}C-NMR (100 MHz, $CDCl_3$): 177.9; 170.4; 79.3; 68.1; 35.7; 30.6; 28.3; 27.4; 21.1; 18.7. HR-EI-MS: 197.1052 ($C_{10}H_{15}NO_3^+$; calc. 197.1052).

Data of Uncyclized Amino Ester: Yellow oil. R_f (AcOEt/MeOH 99:1) 0.5. ^{1}H-NMR (300 MHz, $CDCl_3$): 4.44 (*d*, *J* = 5.5, 1 H); 4.08 (*q*, *J* = 7.0, 2 H); 2.43–2.26 (*m*, 2 H); 2.11–1.99 (*m*, 1 H); 1.93–1.77 (*m*, 6 H); 1.68–1.36 (*m*, 4 H); 1.21 (*t*, *J* = 7.0, 3 H). ^{13}C-NMR (75 MHz, $CDCl_3$): 173.6 (C); 163.8 (C); 87.6 (CH); 81.0 (C); 60.3 (CH_2); 39.13 (CH_2); 34.63 (CH_2); 34.13 (CH_2); 30.13 (CH_2); 23.03 (CH_2); 14.13 (Me); 13.73 (Me). HR-ESI-MS: 266.1375 ($C_{12}H_{21}NNaO_4^+$; calc. 266.1368).

The relative configuration of **5a** was confirmed by converting it to the corresponding ^{t}BuPh$_2$Si-protected compound **5c**: To the soln. of **5a** (60 mg, 0.3 mmol) in MeOH (1.5 ml) was added K_2CO_3 (138 mg, 1.0 mmol), and the mixture was stirred for 18 h at r.t. Upon completion (TLC monitoring), MeOH was evaporated, and the residue was dissolved in DMF (1 ml) and treated with 1*H*-imidazole (45 mg, 0.06 mmol) followed by dropwise addition of ^{t}BuPh$_2$SiCl (84 µl, 0.33 mmol). The mixture was stirred for 4 h at r.t. The soln. was diluted with CH_2Cl_2 and washed with 1N $NaHSO_4$ and brine, dried

(Na_2SO_4), and concentrated. Purification by FC (hexane/AcOEt 99:1) gave **5c** (73 mg, 62% over 2 steps).

*6-{[(*tert*-Butyl)dimethylsilyl]oxy}-1-azaspiro[4.4]nonan-2-one* (**5b**). According to the *General Procedure B*, from *trans*-**4b** (33 mg, 0.1 mmol) and 10% Pd/C (16 mg). Purification by FC (AcOEt) gave **5b** (23 mg, 88%). Pale yellow solid. M.p. 34–36°. R_f (AcOEt) 0.48. IR ($CHCl_3$) 3423, 3018, 1686. ^{1}H-NMR (300 MHz, $CDCl_3$): 5.89 (br. *s*, 1 H); 3.84 (t, J = 7.4, 1 H); 2.49–2.25 (*m*, 3 H); 1.93–1.82 (*m*, 1 H); 1.77–1.48 (*m*, 6 H); 0.87 (*s*, 9 H); 0.04 (*s*, 6 H). ^{13}C-NMR (75 MHz, $CDCl_3$): 178.4; 78.5; 69.1; 35.2; 30.9; 30.8; 27.0; 25.7; 18.0; 17.9; −4.7; −4.9. HR-ESI-MS: 292.1704 ($C_{14}H_{27}NNaO_2Si^+$; calc. 292.1708).

*6-{[(*tert*-Butyl)diphenylsilyl]oxy}-1-azaspiro[4.4]nonan-2-one* (**5c**). According to the *General Procedure B*, from *trans*-**4c** (major diastereoisomer; 300 mg, 0.66 mmol) and 10% Pd/C (100 mg). Purification by FC (AcOEt) gave **5c** (219 mg, 87%). White solid. M.p. 122–124°. R_f (AcOEt) 0.53. IR ($CHCl_3$): 3423, 3017, 1690. ^{1}H-NMR (300 MHz, $CDCl_3$): 7.65–7.63 (*m*, 4 H); 7.45–7.34 (*m*, 6 H); 6.49 (br. *s*, 1 H); 3.91 (*t*, J = 6.6, 1 H); 2.62–2.53 (*m*, 1 H); 2.42–2.24 (*m*, 2 H); 1.82–1.42 (*m*, 7 H); 1.06 (*s*, 9 H). ^{13}C-NMR (75 MHz, $CDCl_3$): 178.0; 135.8; 135.8; 134.1; 133.2; 129.8; 129.7; 127.7; 127.5; 78.6; 69.3; 35.1; 30.7; 30.5; 26.9; 26.8; 19.2; 17.8. HR-ESI-MS: 394.2219 ($C_{24}H_{32}NO_2Si^+$; calc. 394.2202).

*(5*R*,6*S*)-6-{[(*tert*-Butyl)diphenylsilyl]oxy}-1-azaspiro[4.4]nonan-2-one* ((−)-(5*R*,6*S*)-**5c**). According to the procedure reported for racemic **4c**, from (+)-(1*R*,2*S*)-**4c** (300 mg, 0.66 mmol). Purification by FC (AcOEt) gave (−)-(5*R*,6*S*)-**5c** (189 mg, 75%). Viscous oil. $[\alpha]_D^{25} = -19$ (c = 1.0, $CHCl_3$).

*(5*R*)-1-Azaspiro[4.4]nonane-2,6-dione* ((−)-(*R*)-**2**). To a stirred soln. of (−)-(5*R*,6*S*)-**5c** (393 mg, 1.0 mmol) in THF (2 ml) was added 1M Bu_4NF in THF (2.0 ml, 2.0 mmol). The mixture was stirred for 5 h at r.t. and then concentrated. The residue was purified by FC (AcOEt/MeOH 99:1) to obtain the corresponding alcohol (135 mg, 87%) [15][16b]. White solid. R_f (AcOEt) 0.1. ^{1}H-NMR (300 MHz, $CDCl_3$): 7.35 (br. *s*, 1 H); 4.01 (br. *s*, 1 H); 3.94 (*td*, J = 8.1, 3.5, 1 H); 2.52–2.27 (*m*, 3 H); 2.01–1.93 (*m*, 1 H); 1.80–1.53 (*m*, 6 H). ^{13}C-NMR (75 MHz, $CDCl_3$): 179.0; 77.2; 69.2; 35.2; 31.1; 28.9; 26.5; 17.2. HR-EI-MS: 155.0946 ($C_8H_{13}NO_2^+$; calc. 155.0946).

A soln. of the above-described alcohol (39 mg, 0.25 mmol) in CH_2Cl_2 (1 ml) was added dropwise to a slurry of PCC (81 mg, 0.375 mmol, 1.5 equiv.) in CH_2Cl_2 (2 ml). The mixture was stirred for 2 h at r.t. After evaporation, the residue was purified by FC (AcOEt): (−)-(*R*)-**2** (30 mg, 79%). White solid. M.p. 131–133°. ([15]: m.p. 133–134°). $[\alpha]_D^{25} = -65$ (c = 0.46, $CHCl_3$) ([15] and [16a]: $[\alpha]_D^{25} = -68$ (c = 1.0, $CHCl_3$) and −64, resp.). Physical and spectral data: in accordance with [15].

5. *Synthesis of* Mori *Intermediate (−)-***16**. *(+)-3-{[(*tert*-Butyl)dimethylsilyl]oxy}cyclopentane-1,2-diol* (**11**). To a soln. of (−)-(*S*)-(cyclopent-2-en-1-yloxy)(1,1-dimethylethyl)dimethylsilane (=(−)-(3*S*)-3-{[1,1-dimethylethyl)dimethylsilyl]oxy}cyclopentene; **10**) [19] (10.0 g, 50.4 mmol) and trimethylamine *N*-oxide hydrate (8.40 g, 76 mmol) in acetone/H_2O 10:1 (505 ml) was added $K_2Os_4 \cdot H_2O$ (93 mg, 0.25 mmol). The mixture was stirred at r.t. for 6 h. Acetone was evaporated and the crude product poured into sat. aq. $NaHSO_3$ soln. Extraction with Et_2O, drying of the combined org. extract (Na_2SO_4), and concentration afforded a crude product that was purified by FC (pentane/Et_2O 6:4): **11** (9.84 g, 84%). Colorless oil. $[\alpha]_D^{22} = +24.5$ (c = 1.0, $CHCl_3$). IR (film): 3382, 1251, 1053, 833, 774. ^{1}H-NMR (300 MHz, $CDCl_3$): 4.16 (*m*, 1 H); 4.07 (*m*, 1 H); 3.72 (*m*, 1 H); 3.03 (*m*, 2 H); 2.10–1.97 (*m*, 2 H); 1.63–1.52 (*m*, 1 H); 1.46–1.36 (*m*, 1 H); 0.86 (*s*, 9 H); 0.05 (*s*, 3 H); 0.04 (*s*, 3 H). ^{13}C-NMR (75 MHz, $CDCl_3$): 79.5 (CHOSi); 77.4 (CHOH); 71.6 (CHOH); 29.7 (CH_2); 28.9 (CH_2), 25.8 (Me_3C); 18.1 (Me_3C); −4.7 (2 SiMe). EI-MS (70 eV): 231 (15, $[M-H]^+$), 175 (25), 158 (66), 157 (81), 131 (37), 119 (41), 101 (48), 75 (100), 73 (59), 57 (37). HR-EI-MS: 232.14939 ($C_{11}H_{24}O_3Si^+$; calc. 232.14947).

*(+)-Tetrahydro-2,2-dimethyl-4-methylene-*4*H-cyclopenta-1,3-dioxole* (**8**). To a suspension of **11** (600 mg, 2.60 mmol) in 2,2-dimethoxypropane (6.5 ml) was added a catalytic amount of *p*-toluenesulfonic acid (90 mg, 470 μmol). The mixture was stirred at r.t. for 30 min, and 1M NaOH was added. The mixture was extracted with Et_2O, the org. phase washed with H_2O, dried (Na_2SO_4), and concentrated, and the crude product purified by FC (pentane/Et_2O 95:5): corresponding acetonide (670 mg, 95%). Colorless oil. $[\alpha]_D^{22} = +12.4$ (c = 1.0, $CHCl_3$). IR (film): 1068, 1040, 831, 775. ^{1}H-NMR (300 MHz, $CDCl_3$): 4.71 (*m*, 1 H); 4.27 (*dd*, J = 5.64, 1.32, 1 H); 4.09 (*m*, 1 H); 1.97–1.72 (*m*, 3 H); 1.53–1.48 (*m*, 1 H); 1.40 (*s*, 3 H); 1.27 (*s*, 3 H); 0.86 (*s*, 9 H); 0.05 (*s*, 3 H); 0.04 (*s*, 3 H). ^{13}C-NMR (75 MHz, $CDCl_3$): 109.5 (Me_2C); 86.9 (*C*HOC); 80.4 (*C*HOC); 76.9 (CHOSi); 31.1 (CH_2); 30.1 (CH_2); 26.2 (Me); 25.7 (3 Me); 23.9 (Me); 18.0 (Me_3C); −4.8 (Me_2Si); −4.8 (Me_2Si). EI-MS (70 eV): 258 (37, $[M-CH_2]^+$), 158

(67), 157 (100), 127 (54), 101 (68), 75 (93), 73 (56). HR-EI-MS: 272.18093 ($C_{14}H_{28}O_3Si^+$; calc. 272.18077).

To a soln. of the acetonide (670 mg, 2.46 mmol) in THF (5.5 ml) was added 1.0M Bu_4NF in THF (3 ml) dropwise at 0°. After stirring at r.t. for 2 h, the mixture was extracted with Et_2O. The extract was washed with brine, dried (Na_2SO_4), and concentrated, and the crude product purified by FC (pentane/Et_2O 60:40): expected alcohol (345 mg, 89%). White solid. M.p. 63–65°. $[\alpha]_D^{22} = +39.7$ ($c = 1.0$, $CHCl_3$). IR (film): 3415, 1041, 1012. ^{1}H-NMR (300 MHz, $CDCl_3$): 4.74 (*m*, 1 H); 4.33 (*m*, 1 H); 4.14 (*m*, 1 H), 1.97–1.82 (*m*, 4 H); 1.61–1.48 (*m*, 1 H); 1.40 (*s*, 3 H); 1.28 (*s*, 3 H). ^{13}C-NMR (75 MHz, $CDCl_3$): 109.8 (Me_2C); 86.5 (CHO); 80.3 (CHO); 76.5 (CHOH); 30.7 (CH_2); 30.0 (CH_2); 26.1 (Me); 23.8 (Me). EI-MS (70 eV): 158(12), 144 (44), 143 (67), 83 (72), 59 (74), 55 (72). HR-EI-MS: 158.09429 ($C_8H_{14}O_3^+$; calc. 158.09407).

To freshly activated and grounded 3 Å molecular sieve (2 g) in dry CH_2Cl_2 (12 ml) was added the alcohol (400 mg, 2.53 mmol), pyridinium dichromate (927 mg, 4.3 mmol), and anh. AcOH (250 µl). After stirring for 1 h at r.t., the mixture was filtered through a short pad of *Celite*® (Et_2O as eluent). The reddish brown filtrate was evaporated, and toluene was added to the filtrate to remove traces of AcOH by evaporation. The resulting dark brown residue was dissolved in CH_2Cl_2, and AcOEt was added to precipitate the Cr^{III} species. The soln. was filtered through a pad of SiO_2 (Et_2O as eluent). The brownish filtrate was concentrated and the crude product purified by FC (pentane/Et_2O 7:3): tetrahydro-2,2-dimethyl-4*H*-cyclopenta-1,3-dioxol-4-one (395 mg, 79%). White crystals. IR (film): 1736, 903. M.p. 48–50°. $[\alpha]_D^{22} = +41.2$ ($c = 1.0$, $CHCl_3$). ^{1}H-NMR (300 MHz, $CDCl_3$): 4.82 (*t*, $J = 4.62$, 1 H); 4.17 (*d*, $J = 4.85$, 1 H); 2.66–2.52 (*m*, 1 H); 2.32–2.20 (*m*, 2 H); 2.10–1.97 (*m*, 1 H); 1.42 (*s*, 3 H); 1.35 (*s*, 3 H). ^{13}C-NMR (75 MHz, $CDCl_3$): 214.6 (CO); 111.7 (Me_2C); 78.7 (CHO); 77.2 (CHO); 32.8 (CH_2); 26.5 (CH_2); 24.6 (Me); 23.2 (Me). EI-MS (70 eV): 156 (62), 152 (64), 141 (74), 123 (100), 99 (97), 85 (63), 69 (53), 59 (85), 43 (84), 41 (98). HR-EI-MS: 156.07811 ($C_8H_{12}O_3^+$; calc.156.07864).

Methyltriphenylphosphonium bromide (687 mg, 1.92 mmol) and ^{t}BuOK (215 mg, 1.92 mmol) were dissolved in Et_2O (5 ml) and heated at 40° during 1 h. The cyclopentadioxolone (150 mg, 1.28 mmol) in Et_2O (1.33 ml) was added to the yellow suspension, and the soln. was stirred for 2 h at 40°. After cooling, more Et_2O was added and the soln. was washed with H_2O and dried (Na_2SO_4). Evaporation of the solvent afforded a crude product that was purified by FC (pentane/Et_2O 95:5): **8** (177 mg, 90%). Colorless oil. $[\alpha]_D^{22} = +112.5$ ($c = 1.0$, $CHCl_3$). IR (film): 1738, 1366, 905. ^{1}H-NMR (300 MHz, $CDCl_3$): 4.51 (*d*, $J = 2.64$, 1 H); 4.45 (*m*, 1 H); 4.10–4.03 (*m*, 2 H); 2.02–1.89 (*m*, 1 H); 1.55–1.48 (*m*, 1 H); 1.34–1.27 (*m*, 1 H); 1.04–0.90 (*m*, 1 H); 0.82 (*s*, 3 H); 0.69 (*s*, 3 H). ^{13}C-NMR (75 MHz, $CDCl_3$): 150.5 (C=CH_2); 111.5 (C=CH_2); 110.1 (Me_2C); 82.0 (CHO); 80.4 (CHO); 31.1 (CH_2); 29.3 (CH_2); 26.4 (Me); 24.3 (Me). TOF-MS (pos., 70 eV): 177.0889 (2.4, $[M - Na]^+$), 157.0778 (0.6). HR-ESI-MS: 177.0891 ($C_9H_{14}NaO_2^+$; calc. 177.0889).

(+)-4-Azido-tetrahydro-2,2-dimethylcyclopenta-1,3-dioxol-4)-propanic Acid Ethyl Ester (**7**). *Hexabutyldistannane Procedure.* To a stirred soln. of **8** (100 mg, 0.65 mmol) in dry benzene (1.3 ml) were added pyridine-3-sulfonyl azide (360 mg, 1.95 mmol), ethyl iodoacetate (0.77 ml, 0.65 mmol), Bu_3Sn_2 (0.49 ml, 0.97 mmol), and di(*tert*-butyl) hyponitrite (7.34 mg, 0.04 mmol). The resulting mixture was heated reflux and N_2. After 2 h, another portion of di(*tert*-butyl) hyponitrite (7.34 mg, 0.04 mmol) was added, and the mixture was further heated under reflux for 2 h. Upon completion, the solvent was evaporated, the crude product filtered with cyclohexane/^{t}BuOMe 80:20 through SiO_2, the filtrate evaporated, and the crude product purified by FC (SiO_2 mixed with KF [29], cyclohexane/^{t}BuOMe 95:5): **7** (148 mg, 80%).

Et_3B Procedure. Freshly prepared 2M Et_3B in dry EtOH was added *via* syringe pump within 1 h at r.t. to an air-exposed vigorously stirred mixture of **8** (100 mg, 0.65 mmol), pyridine-3-sulfonyl azide (360 mg, 1.95 mmol), and ethyl iodoacetate (0.77 ml, 0.65 mmol) in H_2O (*Caution:* the needle must be immersed into the mixture to avoid a direct contact of Et_3B drops with air). After 1 h, hexane was added, the aq. layer extracted with Et_2O, the combined org. phase washed with H_2O, dried ($MgSO_4$), and concentrated, and the crude product purified by FC (cyclohexane/^{t}BuOMe 95:5): **7** (141 mg, 76%). Colorless oil. $[\alpha]_D^{22} = +145.6$ ($c = 1.0$, $CHCl_3$). IR (film): 2098, 1447, 1160, 1039. ^{1}H-NMR (300 MHz, $CDCl_3$): 4.70–4.67 (*m*, 1 H); 4.17 (*q*, $J = 7.14, 14.31, 21.45$, 2 H); 4.07 (*d*, $J = 5.64$, 1 H); 2.51–2.45 (*m*, 2 H); 2.10–2.04 (*m*, 2 H); 1.81–1.74 (*m*, 4 H); 1.40 (*s*, 3 H); 1.28–1.23 (*m*, 6 H). ^{13}C-NMR (75 MHz, $CDCl_3$):

173.1 (COO); 110.2 (Me_2C); 83.8 (CHO); 80.5 (CHO); 74.0 (CN_3); 60.5 ($MeCH_2O$); 31.9 (CH_2); 30.2 (CH_2); 29.7 (CH_2); 28.5 (CH_2); 26.1 (Me); 23.9 (Me); 14.2 (Me). EI-MS (70 eV): 284 (7, $[M-H]^+$), 268 (71), 183 (72), 169 (83), 152 (76), 123 (81), 100 (82), 96 (100), 81 (96), 69 (96), 56 (87), 39 (89). HR-EI-MS: 283.15334 ($C_{13}H_{21}N_3O_4^+$; calc. 283.15321).

*(+)-(2′*R*,3a*R*,6a*S*)-Tetrahydro-2,2-dimethylspiro[4*H*-cyclopenta-1,3-dioxole-4,2′-pyrrolidin]-5′-one* (**12**). To a stirred soln. of **7** (566 mg, 2.0 mmol) in dry EtOH (8 ml) was added 5% $Pd/CaCO_3$ (60 wt.-%). The mixture was stirred under 30 bar of H_2 for 48 h at 90°. The slurry was filtered through *Celite*®, the solvent evaporated, and the residue purified by FC (AcOEt/EtOH 97.5 : 2.5): **12** (422 mg, > 95%). White solid. M.p. 111–113°. $[\alpha]_D^{22} = +22.8$ ($c = 1.0$, $CHCl_3$). IR (neat): 1688, 1435, 1035, 896. ^{1}H-NMR (300 MHz, $CDCl_3$): 7.22 (*s*, 1 H); 4.75 (*t*, $J = 4.53$, 1 H); 4.23 (*m*, 1 H); 2.46–2.32 (*m*, 3 H); 1.99–1.68 (*m*, 6 H); 1.44 (*s*, 3 H); 1.29 (*s*, 3 H). ^{13}C-NMR (75 MHz, $CDCl_3$): 178.7 (CO); 110.4 (Me_2C); 85.8 (CHO); 80.2 (CHO); 69.2 (CN); 34.7 (CH_2CO); 30.4 (CH_2); 30.3 (CH_2); 26.7 (CH_2); 26.1 (CH_2); 23.9 (Me). B.p. 112–114°. EI-MS (70 eV): 211 (14, M^+), 196 (6), 153 (22), 136 (14), 110 (15), 101 (20), 97 (100), 69 (39), 43 (41) 41 (16). HR-EI-MS: 211.12084 ($C_{11}H_{17}NO_3^+$; calc. 211.12085).

*(+)-(2′*S*,3a*R*,6a*S*)-Tetrahydro-1′-[2-(6-iodo-1,3-benzodioxol-5-yl)ethyl]-2,2-dimethylspiro[4*H*-cyclopenta-1,3-dioxole-4,2′-pyrrolidine]* (**14**). A soln. of **12** (400 mg, 2.0 mmol) in dry benzene (20 ml) was added dropwise to a slurry of sodium bis(2-methoxyethoxy)aluminium hydride (1 ml, 3.80 mmol) in dry benzene (20 ml). The mixture was stirred for 3 h under reflux. After hydrolysis with H_2O and 1M aq. NaOH, the mixture was filtered, the filtrate extracted with Et_2O, and the extract dried (Na_2SO_4) and concentrated spiro[cyclopentadioxol-pyrrolidine] to afford the crude that was used for the next step without further purification. Pale yellow oil. IR (neat): 1693, 1205, 1035. ^{1}H-NMR (300 MHz, $CDCl_3$): 4.73 (*t*, $J = 4.71$, 1 H); 4.03 (*dd*, $J = 5.46, 1.32$, 1 H); 3.04–2.99 (*m*, 1 H); 2.82–2.77 (*m*, 1 H); 2.10–1.48 (*m*, 9 H); 1.42 (*s*, 3 H); 1.28 (*s*, 3 H). ^{13}C-NMR (75 MHz, $CDCl_3$): 109.5 (Me_2C); 85.3 (CHO); 81.0 (CHO); 72.5 (CN); 46.3 (CH_2N); 34.8 (CH_2); 31.3 (CH_2); 30.9 (CH_2); 26.3 (Me); 26.0 (CH_2); 24.0 (Me).

To a stirred soln. of the crude spiro[cyclopentadioxole-pyrrolidine] (395 mg, 2.0 mmol) in dry MeCN (4 ml) were added the 4-nitrobenzenesulfonate **13** (1.12 g, 3.2 mmol) and ^{i}Pr$_2$EtN (4 ml, 8 mmol) at r.t. Stirring was continued under reflux for 20 h, then the mixture was diluted with ^{t}BuOMe and extracted with 1M aq. NaOH. The org. layer was dried (Na_2SO_4), the solvent evaporated, and the residue purified by FC (AcOEt/cyclohexane 85 : 15): **14** (785 mg, 83%). Colorless oil. $[\alpha]_D^{22} = +17.3$ ($c = 1.0$, $CHCl_3$). IR (neat): 1473, 1224, 1036. ^{1}H-NMR (300 MHz, $CDCl_3$): 7.20 (*s*, 1 H); 6.73 (*s*, 1 H); 5.94 (*s*, 2 H); 4.62 (*t*, $J = 12.06, 6.03$, 1 H); 4.26 (*d*, $J = 6.42$, 1 H); 3.03–2.67 (*m*, 4 H); 2.60–2.43 (*m*, 2 H); 2.23–2.14 (*m*, 1 H); 1.85–1.49 (*m*, 7 H); 1.45 (*s*, 3 H); 1.29 (*s*, 3 H). ^{13}C-NMR (75 MHz, $CDCl_3$): 148.4 (CO); 146.9 (CO); 136.4 (C); 118.5 (C); 110.5 (Me_2C); 109.7 (C); 101.5 (CH_2); 87.7 (CHO); 83.7 (CHO); 80.5 (CN); 77.4 (CI); 51.5 (CH_2N); 50.5 (CH_2N); 41.0 (CH_2); 32.5 (CH_2); 31.0 (CH_2); 30.6 (CH_2); 26.3 (Me); 24.3 (Me); 21.8 (CH_2). TOF-MS (pos., 70 eV): 472.0963 (1.2, $[M-H]^+$), 313.2810 (1.1). HR-ESI-MS: 472.0984 ($C_{20}H_{27}INO_4^+$; calc. 472.0963).

*(+)-(2′*S*,3a*R*,6a*S*)-Tetrahydro-1′-[2-(6-Iodo-1,3-benzodioxol-5-yl)ethyl]spiro[4*H*-cyclopenta-1,3-dioxole-4,2′-pyrrolidine]-2-thione* (**15**). Acetonide **14** (200 mg, 424 μmol) was heated under reflux in 2M HCl and 95% EtOH for 2.5 h. Then the solvent was evaporated and the residue purified by FC (Et_2O/NH_3): corresponding diol (160 mg, 88%). Viscous oil. $[\alpha]_D^{22} = +24.8$ ($c = 1.0$, $CHCl_3$). IR (neat): 3388, 1472, 1225, 1036. ^{1}H-NMR (300 MHz, $CDCl_3$): 7.22 (*s*, 1 H); 6.75 (*s*, 1 H); 5.94 (*s*, 2 H); 4.13–4.08 (*dt*, $J =$ 11.85, 5.82, 2.43, 1 H); 3.80 (*d*, $J = 6.42$, 1 H); 3.32–3.25 (*m*, 1 H); 2.90–2.41 (*m*, 7 H); 2.21–2.11 (*m*, 1 H); 1.96–1.78 (*m*, 3 H); 1.63–1.47 (*m*, 4 H). ^{13}C-NMR (75 MHz, $CDCl_3$): 148.5 (CO); 147.0 (CO); 136.1 (C); 118.6 (C); 109.7 (C); 101.6 (CH_2O); 87.7 (CHO); 77.2 (CHO); 73.7 (CI); 70.1 (CN); 51.9 (CH_2N); 49.3 (CH_2N); 40.3 (CH_2); 32.0 (CH_2); 29.2 (CH_2); 25.8 (CH_2); 21.6 (CH_2). HR-ESI-MS: 432.0671 ($C_{17}H_{23}INO_4^+$; calc. 432.0681).

To a stirred soln. of diol (566 mg, 1.30 mmol) in dry CH_2Cl_2 (5 ml) was added 1,1′-(thiocarbonyl)-bis[1*H*-imidazole] (= di-1*H*-imidazol-1-ylmethanethione; 715 mg, 4.0 mmol) and ^{i}Pr$_2$EtN (15 μl, 13 mmol). The mixture was stirred under reflux for 5 h and then diluted with CH_2Cl_2. The CH_2Cl_2 phase was washed with H_2O, dried (Na_2SO_4), and concentrated and the residue subjected to FC (AcOEt/EtOH 97.5 : 2.5): **15** (474 mg, 77%). Colorless liquid. $[\alpha]_D^{22} = +114.3$ ($c = 1.0$, $CHCl_3$). IR (neat): 1472, 1277, 1223. ^{1}H-NMR (300 MHz, $CDCl_3$): 7.20 (*s*, 1 H); 6.69 (*s*, 1 H); 5.94 (*s*, 2 H); 5.22 (*m*, 1 H); 4.82 (*d*, $J = 6.42$, 1 H); 3.50–2.46 (*m*, 6 H); 2.17–1.60 (*m*, 8 H). ^{13}C-NMR (75 MHz, $CDCl_3$): 191.4 (CS); 148.4

(CO); 147.0 (CO); 135.7 (C); 118.5 (C); 109.8 (C); 101.6 (CH_2O); 89.6 (CO); 87.6 (CO); 86.7 (CI); 75.4 (CN); 51.4 (CH_2N); 50.0 (CH_2N); 40.7 (CH_2); 32.1 (CH_2); 31.1 (CH_2); 29.4 (CH_2); 21.9 (CH_2). EI-MS (70 eV): 474 (12, $[M-H]^+$), 473 (46, M^+), 396 (64), 274 (68), 212 (100), 168 (94), 96 (83). HR-ESI-MS: 474.0236 ($C_{18}H_{21}INO_4S^+$; calc. 474.0221).

*(−)-(5*R*)-1-[2-(6-Iodo-1,3-benzodioxol-5-yl)ethyl]-1-azaspiro[4.4]non-6-en-2-one* (**6**). Thione **15** (300 mg, 634 µmol) was heated at 40° in neat 1,3-dimethyl-2-phenyl-1,3,2-diazaphospholidine (420 µl, 1.9 mmol) for 4 h. Then the solvent was evapoarated and the residue purified by FC (AcOEt/EtOH 95 : 5): **6** (217 mg, 83%). Colorless liquid. $[\alpha]_D^{22} = -74.0$ ($c = 1.0$, $CHCl_3$); [23]: $[\alpha]_D^{22} = -32.0$ ($c = 0.08$, $CHCl_3$)). Spectral data: in accordance with [6j][7d][23]. ^{1}H-NMR (300 MHz, $CDCl_3$): 7.20 (*s*, 1 H); 6.74 (*s*, 1 H); 5.92 (*s*, 2 H); 5.82–5.78 (*m*, 1 H); 5.58–5.54 (*m*, 1 H); 3.01–2.94 (*m*, 1 H); 2.84–2.78 (*m*, 3 H); 2.47–2.36 (*m*, 2 H); 2.35–2.27 (*m*, 2 H); 1.90–1.75 (*m*, 5 H); 1.68–1.58 (*m*, 1 H). ^{13}C-NMR (75 MHz, $CDCl_3$): 148.5 (C); 147.0 (C); 135.9 (C); 134.3 (C); 132.6 (C); 118.6 (C); 109.7 (C); 101.5 (CH_2O); 89.0 (CI); 78.8 (C); 51.4 (CN); 50.1 (CH_2); 40.8 (CH_2); 38.8 (CH_2); 31.7 (CH_2); 30.0 (CH_2); 21.8 (CH_2).

*(3a*S*,14b*S*)-3,5,6,8,9,14b-Hexahydro-4*H*-cyclopenta[*a*][1,3]dioxolo[4,5-*h*]pyrrolo[2,1-*b*][3]benzazepine* (*=2,3-Didehydro-2-demethoxy-3-deoxy-1,2-dihydrocephalotaxine*; (−)-**16**). According to the procedure reported by *Tietze*, *Yoshida* and co-workers [7b][7d]: A mixture containing MeCN (5 ml), DMF (5 ml), H_2O (1 ml), **6** (150 mg, 510 µmol), Bu_4NOAc (301 mg, 1.0 mmol), and palladium catalyst (18 mg, $2 \cdot 10^{-2}$ mmol) was stirred for 7 h at 120°. The soln. was poured into ^{t}BuOMe and washed with dil. aq. NaOH soln. The org. layer was extracted with HCl soln. The acidic phase was basified with NaOH and extracted with ^{t}BuOMe. The combined org. layer was dried (Na_2SO_4) and concentrated. Purification by FC (AcOEt) gave *Mori*'s intermediate (−)-**16** (68.4 mg, 46%) [6d][6j][7b][7d][7e]. Colorless liquid. Physical and spectral data: in accordance with [6d]. $[\alpha]_D^{22} = -196.7$ ($c = 1.0$, $CHCl_3$) ([6d]: −230.8 ($c =$ 1.22, $CHCl_3$); [7b]: −200.4 ($c = 1.0$, $CHCl_3$); [6j]: −210.5 ($c = 0.25$, $CHCl_3$)). ^{1}H-NMR (300 MHz, $CDCl_3$): 6.63 (*s*, 1 H); 6.58 (*s*, 1 H); 5.87 (*s*, 1 H); 5.86 (*s*, 1 H); 5.78 (*dddd*, $J = 5.9, 2.6, 2.9, 2.2$, 1 H); 5.52 (*dddd*, $J = 5.9, 2.6, 2.9, 2.2$, 1 H); 3.85 (*m*, 1 H); 3.21 (*m*, 1 H); 3.08 (*m*, 1 H); 2.98–2.75 (*m*, 2 H); 2.60 (*d*, 1 H); 2;45 (*m*, 1 H); 2.36 (*d*, 1 H); 1.58 (*m*, 1 H). ^{13}C-NMR (75 MHz, $CDCl_3$): 148.2 (C); 147.1 (C); 134.5 (C); 133.6 (C); 132.9 (C); 129.1 (C); 110.9 (C); 110.0 (C); 101.5 (CH_2O); 69.5 (C); 63.2 (CN); 54.6 (CH_2); 50.0 (C); 43.6 (CH_2); 35.9 (CH_2); 31.3 (CH_2); 20.5 (CH_2).

REFERENCES

[1] L. Huang, Z. Xue, in 'The Alkaloids', Vol. 23, Academic Press, New York, 1984, p. 157; M. A. Jalil Miah, T. Hudlicky, J. W. Reed, in 'The Alkaloids', Vol. 51, Ed. A. Brossi, Academic Press, New York, 1998, p. 199; H. Abdelkafi, B. Nay, *Nat. Prod. Rep.* **2012**, *29*, 845.

[2] J. Auerbach, S. M. Weinreb, *J. Am. Chem. Soc.* **1972**, *94*, 7172.

[3] M. F. Semmelhack, B. P. Chong, L. D. Jones, *J. Am. Chem. Soc.* **1972**, *94*, 8629; M. F. Semmelhack, B. P. Chong, R. D. Stauffer, T. D. Rogerson, A. Chong, L. D. Jones, *J. Am. Chem. Soc.* **1975**, *97*, 2507.

[4] T. Taniguchi, H. Ishibashi, *Org. Lett.* **2008**, *10*, 4129.

[5] L. F. Tietze, H. Braun, P. L. Steck, S. A. A. El Bialy, N. Tölle, A. Düfert, *Tetrahedron* **2007**, *63*, 6437.

[6] a) M. E. Kuehne, W. H. Parsons, *J. Org. Chem.* **1977**, *42*, 3408; b) M. E. Kuehne, W. G. Bornmann, W. H. Parsons, T. D. Spitzer, J. F. Blount, J. Zubieta, *J. Org. Chem.* **1988**, *53*, 3439; c) C. K. Sha, J. J. Young, C. P. Yeh, S. C. Chang, S. L. Wang, *J. Org. Chem.* **1991**, *56*, 2694; d) N. Isono, M. Mori, *J. Org. Chem.* **1995**, *60*, 115; e) L. Planas, J. Pérard-Viret, J. Royer, *J. Org. Chem.* **2004**, *69*, 3087; f) C.-L. Deng, R.-J. Song, S.-M. Guo, Z.-Q. Wang, J.-H. Li, *Org. Lett.* **2007**, *9*, 5111; g) S. Gao, H.-Y. Liu, Y.-H. Wang, H.-P. He, J.-S. Wang, Y.-T. Di, C.-S. Li, X. Fang, X.-J. Hao, *Org. Lett.* **2007**, *9*, 3453; h) Y.-T. Di, H.-P. He, Y.-S. Wang, L.-B. Li, Y. Lu, J.-B. Gong, X. Fang, N.-C. Kong, S.-L. Li, H.-J. Zhu, X.-J. Hao, *Org. Lett.* **2007**, *9*, 1355; i) W.-D. Z. Li, X.-W. Wang, *Org. Lett.* **2007**, *9*, 1211; j) A. Hameed, A. J. Blake, C. J. Hayes, *J. Org. Chem.* **2008**, *73*, 8045; k) N. Y. Kuznetsov, G. D. Kolomnikova, V. N. Khrustalev, D. G. Golovanov, Y. N. Bubnov, *Eur. J. Org. Chem.* **2008**, 5647.

[7] a) L. F. Tietze, H. Schirok, *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 1124; b) L. F. Tietze, H. Schirok, *J. Am. Chem. Soc.* **1999**, *121*, 10264; c) M. Ikeda, S. A. A. El Bialy, K. Hirose, M. Kotake, T. Sato, S. M. M. Bayomi, I. A. Shehata, A. M. Abdelal, L. M. Gad, T. Yakura, *Chem. Pharm. Bull.* **1999**, *47*,

983; d) S. Suga, M. Watanabe, J. Yoshida, *J. Am. Chem. Soc.* **2002**, *124*, 14824; e) Q. Liu, E. M. Ferreira, B. M. Stoltz, *J. Org. Chem.* **2007**, *72*, 7352; f) W. R. Esmieu, S. M. Worden, D. Catterick, C. Wilson, C. J. Hayes, *Org. Lett.* **2008**, *10*, 3045; g) Q.-W. Zhang, K. Xiang, Y.-Q. Tu, S.-Y. Zhang, X.-M. Zhang, Y.-M. Zhao, T.-C. Zhang, *Chem. – Asian J.* **2012**, *7*, 894.

[8] Y.-M. Zhao, P. Gu, H.-J. Zhang, Q.-W. Zhang, C.-A. Fan, Y.-Q. Tu, F.-M. Zhang, *J. Org. Chem.* **2009**, *74*, 3211.

[9] W.-D. Z. Li, W.-G. Duo, C.-H. Zhuang, *Org. Lett.* **2011**, *13*, 3538.

[10] a) P. Renaud, C. Ollivier, P. Panchaud, *Angew. Chem., Int. Ed.* **2002**, *41*, 3460; b) P. Panchaud, L. Chabaud, Y. Landais, C. Ollivier, P. Renaud, S. Zigmantas, *Chem. – Eur. J.* **2004**, *10*, 3606; c) P. Panchaud, C. Ollivier, P. Renaud, S. Zigmantas, *J. Org. Chem.* **2004**, *69*, 2755; d) G. Lapointe, A. Kapat, K. Weidner, P. Renaud, *Pure Appl. Chem.* **2012**, *84*, 1633.

[11] P. Schär, P. Renaud, *Org. Lett.* **2006**, *8*, 1569; K. Weidner, A. Giroult, P. Panchaud, P. Renaud, *J. Am. Chem. Soc.* **2010**, *132*, 17511.

[12] G. Lapointe, K. Schenk, P. Renaud, *Org. Lett.* **2011**, *13*, 4774.

[13] L. Chabaud, Y. Landais, P. Renaud, *Org. Lett.* **2005**, *7*, 2587.

[14] A. Kapat, E. Nyfeler, G. T. Giuffredi, P. Renaud, *J. Am. Chem. Soc.* **2009**, *131*, 17746; G. Lapointe, K. Schenk, P. Renaud, *Chem. – Eur. J.* **2011**, *17*, 3207.

[15] T. Nagasaka, H. Sato, S. Saeki, *Tetrahedron: Asymmetry* **1997**, *8*, 191.

[16] a) L. Planas, J. Pérard-Viret, J. Royer, M. Selkti, A. Thomas, *Synlett* **2002**, 1629; b) M. Pizzonero, F. Dumas, J. d'Angelo, *Heterocycles* **2005**, *66*, 31.

[17] S. Cren, P. Schär, P. Renaud, K. Schenk, *J. Org. Chem.* **2009**, *74*, 2942.

[18] K. Burgess, L. D. Jennings, *J. Am. Chem. Soc.* **1991**, *113*, 6129.

[19] M. G. Gonçalves-Martin, A. Saxer, P. Renaud, *Synlett* **2009**, 2801.

[20] D. Seebach, A. R. Sting, M. Hoffmann, *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 2708.

[21] P. Panchaud, P. Renaud, *J. Org. Chem.* **2004**, *69*, 3205.

[22] E. J. Corey, P. B. Hopkins, *Tetrahedron Lett.* **1982**, *23*, 1979.

[23] Z. Zhao, P. S. Mariano, *Tetrahedron* **2006**, *62*, 7266.

[24] W. A. Herrmann, C. Brossmer, K. Öfele, C.-P. Reisinger, T. Priermeier, M. Beller, H. Fischer, *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 1844.

[25] A. S. Dreiding, J. A. Hartman, *J. Am. Chem. Soc.* **1953**, *75*, 939; L. M. Konzelman, R. T. Conley, *J. Org. Chem.* **1968**, *33*, 3828.

[26] K. Kikukawa, K. Sakai, K. Asada, T. Matsuda, *J. Organomet. Chem.* **1974**, *77*, 131.

[27] K. Ikura, I. Ryu, N. Kambe, N. Sonoda, *J. Am. Chem. Soc.* **1992**, *114*, 1520; R. J. Fox, G. Lalic, R. G. Bergman, *J. Am. Chem. Soc.* **2007**, *129*, 14144.

[28] R. W. Hoffmann, S. Goldmann, N. Maak, R. Gerlach, F. Frickel, G. Steinbach, *Chem. Ber.* **1980**, *113*, 819.

[29] D. C. Harrowven, I. L. Guy, *Chem. Commun.* **2004**, 1968.

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