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Use of epoxidation and epoxide opening reactions for the synthesis of highly functionalized 1-oxaspiro[4.5]decan-2-ones and related compounds

Martin Eipert,[a] Cäcilia Maichle-Mössmer[b] and Martin E. Maier[a,*]

[a]*Institut für Organische Chemie, Universität Tübingen, Auf der Morgenstelle 18, 72076 Tübingen, Germany*
[b]*Institut für Anorganische Chemie, Universität Tübingen, Auf der Morgenstelle 18, 72076 Tübingen, Germany*

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Abstract—Epoxidation of ethyl 3-(6-hydroxycyclohex-1-en-1-yl)propanoate (**11**) provided the *syn* epoxide **12**. By invoking chelation controlled epoxide opening the triol derivatives **13** and **14** or the spiro lactone **25** could be obtained. Elimination of HBr from the bromides **26** and **27** produced the spiro cyclohexenones **28** and **29**. Epoxidation of the double bond occurred in a diastereoselective manner to give epoxides **30** and **31**, respectively. Treatment of the epoxide **31** with LiBr/AcOH gave the bromo hydrin **38**. In a 'merry go round' fashion **38** was further functionalized on the cyclohexane ring by elimination, epoxidation, and epoxide opening resulting in the bromo hydrin **43**. Other cyclohexane derivatives that were produced during these studies include the cyclohexenone **19** and the cyclohexanediol **23**. In addition, enolate azidation of the spiro lactone **29** proceeded in a diastereoselective manner providing the α-azido lactone **32**.

1. Introduction

A range of natural products contains a spiro lactone subunit. This structure contributes to a unique shape of the corresponding molecules and can also be essential for biological activity if an α-methylene lactone is present that can function as a Michael acceptor. Some representative examples include the terpene pathylactone (**1**),[1] the iridoid gaertneroside (**2**),[2] or some synthetic spiro lactones, such as **3**[3] and **4**[4] that were designed to restrict the conformational flexibility in the carbocyclic sector (Fig. 1). In synthetic approaches to spiro lactones one starts, as with any bicyclic ring system, with one of the two rings to which the second one is attached. This can be achieved by some kind of cyclization or rearrangement reaction.[5]

A special type of spiro lactones are spiro[4,5]decanes with a highly functionalized cyclohexane ring. This class of compounds encompasses several biologically active compounds such as aranorosin (**5**),[6] or some analogs thereof that function as HMG-CoA synthase inhibitors or antifungal agents. Another similar compound, although lacking the spiro lactone is scyphostatin (**6**) which possesses inhibitory activity against a neutral sphingomyelinase.[7,8] The biosynthesis and also some synthetic strategies to these compounds rely on the oxidation of tyrosine derivatives. For example, treatment of *N*-protected tyrosine **7** with the iodine reagent $PhI(OAc)_2$ afforded the spirolactone **8** (40% yield).[6a] While these oxidizing reactions deliver the spiro system very efficiently, the corresponding ortho dienones are susceptible to side reactions such as dimerization or elimination reactions upon further derivatization (Fig. 2).[9]

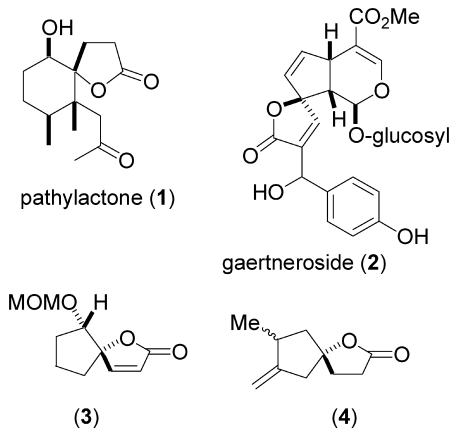

Figure 1. Some natural products and synthetic intermediates containing a spiro lactone subunit.

2. Results

Therefore we opted for a different strategy to spiro[4.5]-decanes that relies on the opening of a cyclohexane epoxide carrying a suitable side chain. In this paper we report on some feasibility studies that led to some unexpected results.

Keywords: epoxidation; 1-oxaspiro[4.5]decan-2-ones; Michael acceptor.
* Corresponding author. Tel.: +49-7071-29-75247; fax: +49-7071-29-5137; e-mail: martin.e.maier@uni-tuebingen.de

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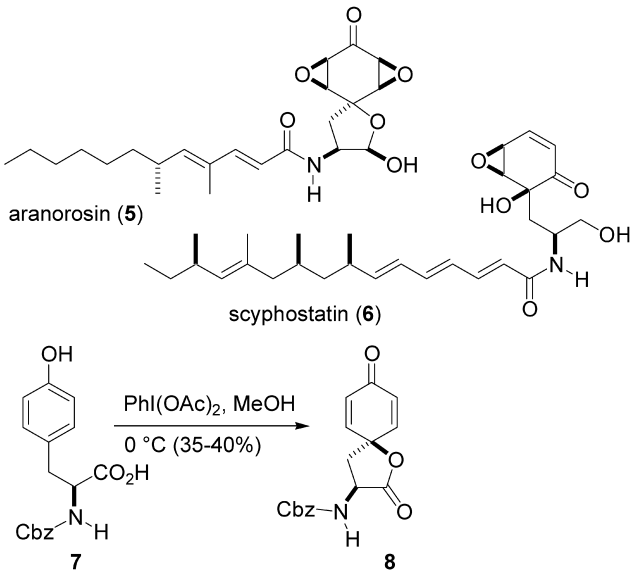
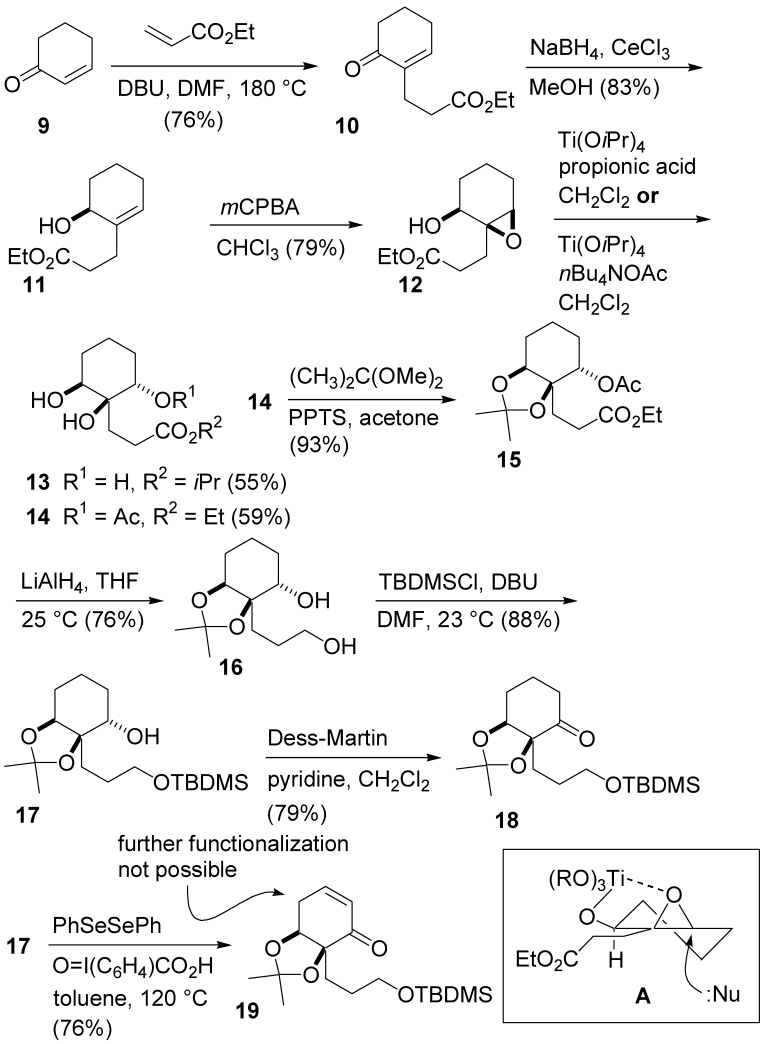


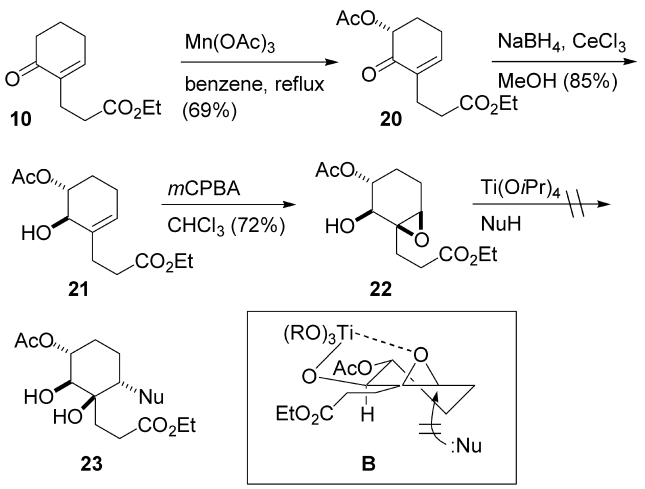
Figure 2. Natural products with a highly functionalized cyclohexane epoxide substructure.

Initial studies focused on the regiochemistry of epoxide opening of 2,3-epoxycyclohexan-1-ol carrying an ester side chain in the 2-position. The corresponding substrate, the epoxide **12** was prepared from cyclohexenone (**9**) by a Baylis–Hillman type Michael addition to ethyl acrylate yielding the enone **10**.[10] Subsequent Luche reduction[11] gave the allylic alcohol **11** whose directed epoxidation provided the epoxy alcohol **12**. In the presence of a stochiometric amount of $Ti(OiPr)_4$ the nucleophile could be steered to the 3-position of the epoxy alcohol. This is attributed to complexation of the titanium between the alcohol and the epoxy oxygen as shown in complex **A**.[12] This way the triol **13** and the acetate **14** could be obtained (Scheme 1). The *cis*-position of the two hydroxy functions was proven by acetalization providing compound **15**. Treatment of **15** with $LiAlH_4$ led to the diol **16** whose primary hydroxy group was protected as silyl ether. Oxidation of **17** gave the ketone **18**. Alternatively, treatment of **17** with iodosobenzoic acid and diphenyl diselenide effected oxidation to the enone **19**.[13,14]

In order to reach the functionalization level of scyphostatin, a modification of the γ-position of the enone would be necessary. However, attempts toward this goal by radical bromination etc. met with failure. Therefore this position was functionalized on the enone **10** by a manganese



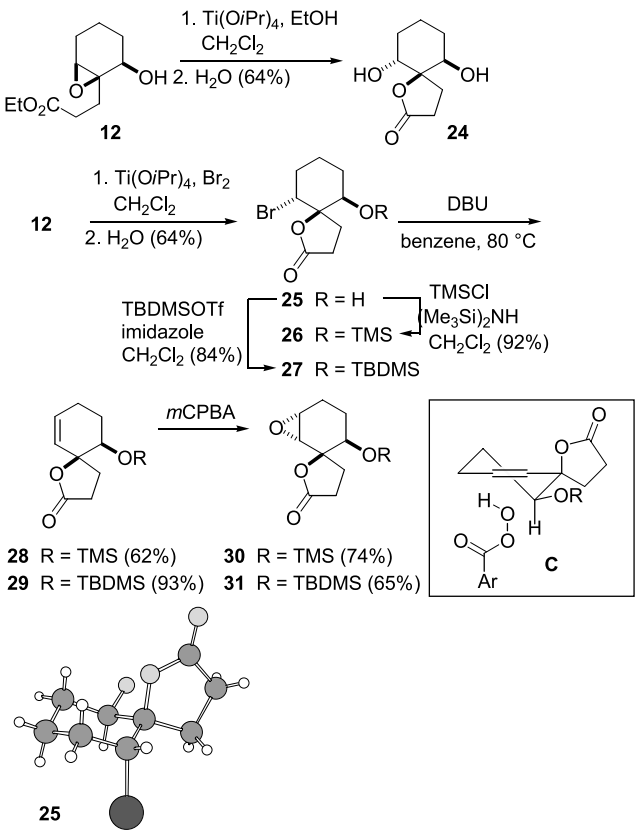
Scheme 1. Synthesis of the epoxide **12**, its opening to the triol derivatives **13** and **14**, and the synthesis of compounds **18** and **19**.



Scheme 2. Acetoxylation of cyclohexenone **10** and synthesis of the epoxide **22**. Attempted opening of epoxide **22**.

triacetate mediated α-acetoxylation to give compound **20**.[15] This was followed by Luche reduction to the allylic alcohol **21** and subsequent epoxidation with *meta* chloroperbenzoic acid resulting in the epoxy alcohol **22**. However, in this case the Ti(O*i*Pr)$_4$ induced epoxide opening did not work. The reason for this failure is not known but it might be speculated that conformational reasons are responsible (Scheme 2).

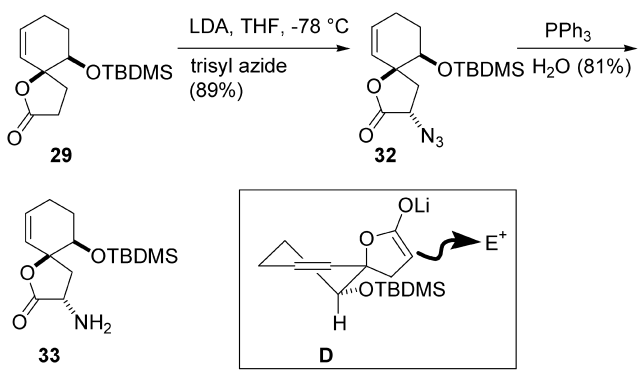
Accordingly, we turned back to substrate **12** subjecting it to different conditions. Thus, the combination of Ti(O*i*Pr)$_4$ and ethanol in CH_2Cl_2 gave rise to the spiro lactone **24** (Scheme 3). The formation of this compound can be explained by epoxide opening with water during the quenching process followed by lactonization. In a similar fashion the combination of Ti(O*i*Pr)$_4$ with bromine furnished the spiro lactone **25**. This result supports the notion that formation of **24** does not proceed by attack of the carboxylic group at the quaternary carbon (C-2). The presence of nine signals in the ^{13}C NMR spectrum of **24** is proof of the unsymmetrical structure. The X-ray structure of spiro lactone **25** is included in Scheme 3, showing the axial orientation of the C–Br and C–O (lactone) bonds.[16] Continuing with the bromo alcohol **25**, silylation to **26** and **27**, respectively, followed by HBr elimination using DBU in benzene produced the cyclohexenes **28** and **29**. These compounds could be converted to the epoxides **30** and **31**. Attack of the perbenzoic acid *anti* to the lactone C–O bond shows that mainly steric effects govern the epoxidation. In the depicted model **C** the peracid even has to approach *anti* to an acceptor bond.



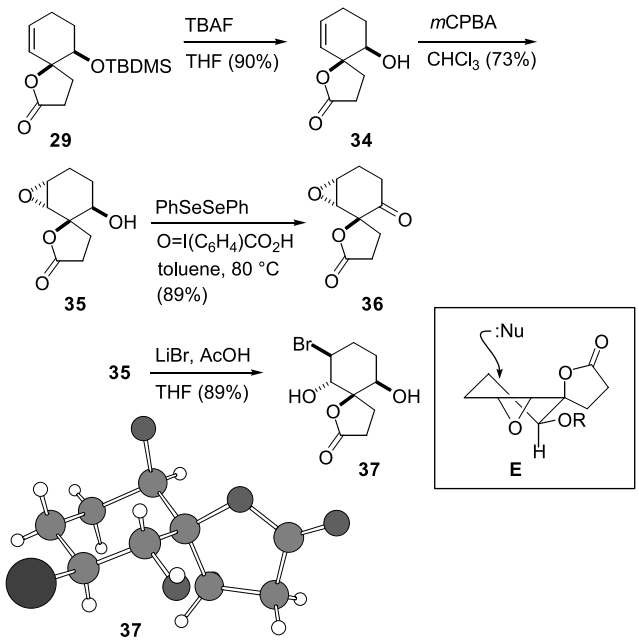
Scheme 3. Conversion of the epoxy alcohol **12** to the spiro compounds **28**–**31**. X-Ray structure of lactone **25**.

Another departure from the spiro compound **29** was the introduction of an amino group in α-position of the lactone. This was achieved by electrophilic azidation of the lithium enolate of **29** with 2,4,6-triisopropylbenzenesulfonyl azide (Scheme 4).[17] While only one diastereomer **32** was formed, its relative configuration could not be assigned, but we assume that the electrophile enters *anti* to the OTBDMS group (cf. model **D**).[18] Treatment of the azide **32** with triphenylphosphine and water gave the amino lactone **33**. Acylation of **33** could provide simplified scyphostatin analogs.

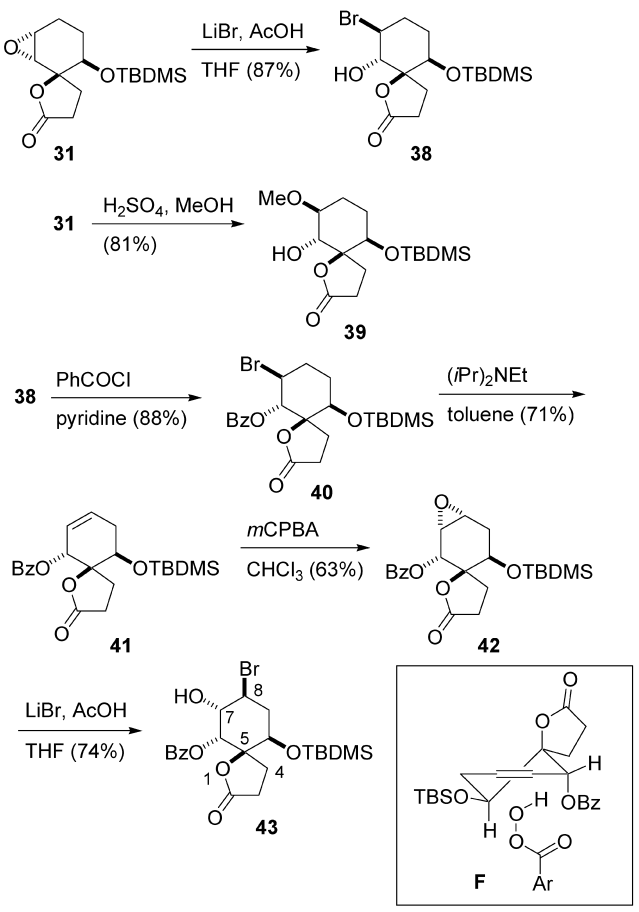
The stereochemical course of the epoxidation of the double bond in the spiro lactone is not changed by a free hydroxy group. Thus, epoxidation of the alkenol **34**, obtained by cleavage of the silyl ether **29** gave the epoxide **35**, with the epoxide being *anti* to the lactone C–O bond (Scheme 5). The epoxy alcohol **35** was oxidized to the epoxy ketone **36** using iodosobenzoic acid in presence of diphenyldiselenide.[13] Alternatively, treatment of the epoxide **35** with lithium bromide/acetic acid in THF caused a regiospecific opening of the epoxide leading to the bromo hydrin **37**. The structure of this compound was secured by X-ray analysis (Scheme 5) which proves also the relative configuration of related precursors.[16]



Scheme 4. Diastereoselective azidation of the lactone **29** yielding amine **33**.



Scheme 5. Deprotection of silyl ether **29** to cyclohexenol **34**, followed by diastereoselective epoxidation to **35** and oxidation to cyclohexanone **36**. Opening of the epoxide **35** to give the bromo hydrin **37**.



Scheme 6. 'Merry go round' functionalization of the cyclohexane ring of **31** by epoxide opening, elimination, epoxidation, and epoxide opening providing bromo hydrin **43**.

In a similar manner to the transformation before, epoxide opening of **31** gave the bromo hydrin **38** and the alcohol **39**, respectively (Scheme 6). The bromo atom serves as a handle to introduce a further functionalization site. Thus, benzoylation of **38** followed by elimination of HBr with Hünig's base led to the highly functionalized spiro cyclohexene **41**. Epoxidation of the double bond occurred in a diastereospecific manner yielding compound **42**. Due to stereoelectronic reasons the epoxide opening occurred selectively at C-8 (product numbering).

3. Discussion

In order to rationalize the formation of the various cyclohexane and cyclohexene derivatives one has to address the issues of diastereoselective epoxidation and the regioselectivity of the epoxide opening. The epoxidation is governed on the one hand by steric effects.[19] On the other hand this inherent selectivity can be reinforced or compromised by directing groups like hydroxyl.[20] Some examples from the literature[19,6a,8g] that serve to illustrate these points are depicted in Figure 3.

The regiochemistry of the opening of cyclohexene derived epoxides is mainly controlled by the Fürst–Plattner rule. This rule calls for a trans-diaxial opening. The consequence of this is that high regioselectivity can be realized if it is possible to channel the opening through only one of the two possible half chair conformations. In these instances as well for acyclic epoxides, chelation control or the formation of ate-complexes is an important strategy for controlling the regiochemistry.[21] Again, this is illustrated with some literature examples (Fig. 4). Thus, if a hydroxyl or hydroxymethyl group is present on the same side of the epoxide, a chelate may form in presence of a Lewis acid or a metal cation. This seems to favor the opening through one of the half chair conformers. For example, treatment of the *cis*-epoxide derived from 3-[(benzyloxy)methyl]cyclohexene with nucleophiles (X=Cl, OCH_3, N_3, CH_3, H) gave predominantly attack on the C-1 oxirane carbon (example 1).[22] The reaction is much less selective with the corresponding *trans* epoxide. In a similar manner the complexation effect [Ti(O*i*Pr)$_4$, I_2] guarantees a regioselective ring opening for the *cis* epoxide derived from 3-cyclohexenol (example 2).[23]

If there is an ester group in proximity to the epoxide this group can be engaged in the epoxide opening or form a lactone after opening of the epoxide. For example, reaction of the epoxide **N** with $HClO_4$ in THF/H_2O gave the *trans* diol **O** that cyclized to the lactone **P**.[24] Under different

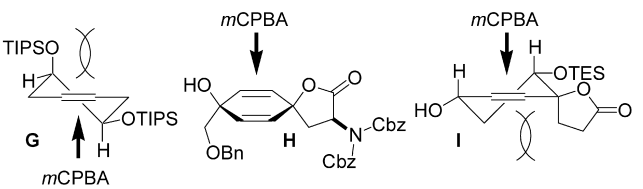


Figure 3. Steric and directing group control of diastereoselective epoxidation of cyclohexene derivatives.

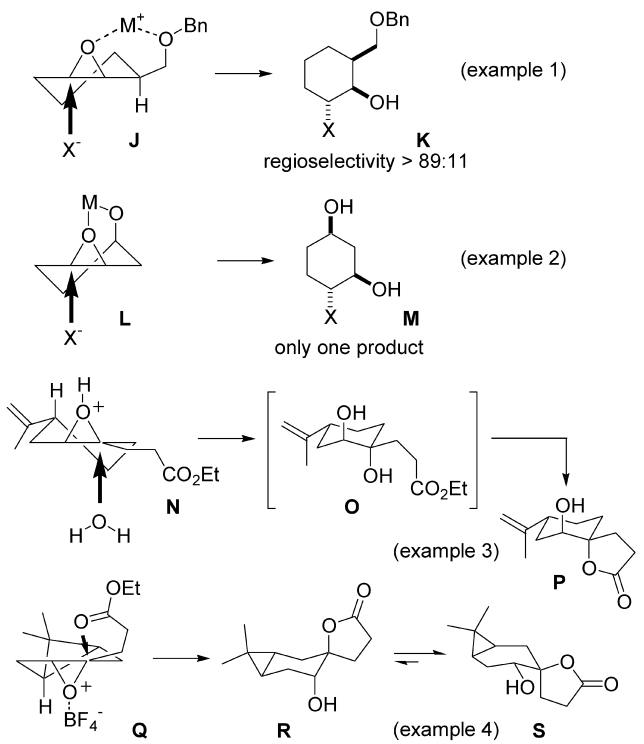


Figure 4. Regiochemistry of epoxide opening in cyclohexane epoxides.

conditions ($BF_3{\cdot}Et_2O$ in toluene) the epoxy ester **Q** cyclized via direct participation of the ester group providing lactone **S**.[25]

Accordingly, the diastereoselective reactions presented in this paper can be summarized as follows. The epoxidation reactions leading to epoxy alcohols **12** and **22** are the result of the directing effect of the hydroxyl group. The epoxidation of the spiro lactones **28**, **29**, and **34** are influenced by steric effects (equatorial alkoxy substituent plus minimal steric interaction with the spiro lactone). For the epoxidation of the lactone **41** a directing effect of the axial benzoate group cannot be ruled out.

The opening of the epoxide **12** can be rationalized by invoking a chelation effect (conformer **A**, Scheme 1). The opening of epoxides **31**, **35**, and **42** proceeds through the most favored conformer. The conformation of these compounds is characterized by one equatorial alkoxy group having the alkyl part of the spiro lactone in equatorial position.

In summary, we present a concise synthesis of the cyclohexene epoxide **12** that served as an entry point to spiro lactones such as **25** or **28**. The cyclohexyl bromide **38** obtained by epoxide opening allowed for further functionalization reactions of the cyclohexane ring via elimination to the unsaturated spiro lactone **41**. Highly functionalized spiro lactones such as **31**, **32**, **35**, **36**, or **42** can serve as interesting scaffolds for combinatorial chemistry and diversity oriented synthesis. In the course of these studies we found further support for the strong directing effect of chelating Lewis acids on the regiochemistry of the opening of epoxy alcohols.

4. Experimental

4.1. General

^1H and ^{13}C NMR: Bruker Avance 400, spectra were recorded either in $CDCl_3$, acetone-d_6 or C_6D_6; chemical shifts are calibrated to the residual proton and carbon resonance of the solvent: $CDCl_3$ (δ_H 7.25, δ_C 77.00 ppm), acetone-d_6 (δ_H 2.095, δ_C 30.60, 205.87 ppm), C_6D_6 (δ_H 7.15, δ_C 128.62 ppm). Melting points: Büchi Melting Point B-540, uncorrected. IR: Jasco FT/IR-430. EI-MS: Finnigan Triple-Stage-Quadrupol (TSQ-70). HRMS (FT-ICR): Bruker Daltonic APEX 2 with electron spray ionization (ESI). Flash chromatography: J. T. Baker silica gel 43–60 μm. Thin-layer chromatography Machery-Nagel Polygram Sil G/UV_{254}. Solvents were distilled prior to use; petroleum ether with a boiling range of 40–60°C was used. Reactions were generally run under a nitrogen atmosphere. Compounds **10** and **11** were prepared according to the literature.[10,11a]

4.2. General procedure 1 for *cis* epoxidation of cyclohexyl allyl alcohols

To a well stirred solution of the allyl alcohol (1 equiv.) in dry $CHCl_3$ (4 mL/mmol) containing $MgSO_4$ (0.08 g/mmol) was added *m*CPBA (1.1 equiv.) in small portions within 10–15 min. The resulting suspension was stirred for 2 h at room temperature, before cyclohexene (1 mL/mmol) was added and the mixture stirred for an additional hour. The white suspension was diluted with diethyl ether (7 mL/mmol), filtered, washed twice with satd. $NaHCO_3$ solution (3 mL/mmol), water and brine. The organic layer was dried over $MgSO_4$, filtered, and concentrated in vacuo.

4.2.1. *rel* Ethyl 3-[(1*S*,2*S*,6*R*)-2-hydroxy-7-oxabicyclo[4.1.0]hept-1-yl]propanoate (12). Starting from alkenol **11** (1.0 g, 5.04 mmol) a yellow oil is obtained according to general procedure 1. The crude product was purified by flash chromatography (petroleum ether/diethyl ether, 2:3) providing the epoxide **12** (0.85 g, 79%) as a colorless oil. TLC (hexane/diethyl ether, 2:3): R_f=0.35; ^1H NMR (acetone-d_6): δ 1.08 (t, J=7.1 Hz, 3H, CH_3), 1.28–1.37 (m, 4H, CH_2), 1.65–1.71 (m, 3H, CH_2), 2.03–2.09 (m, 1H, CH_2), 2.24–2.29 (m, 2H, CH_2), 2.93 (d, J=4.0 Hz, 1H, epoxide-H), 3.74–3.77 (m, 1H, C*H*OH), 3.95 (q, J=7.1 Hz, 2H, CH_2); ^{13}C NMR (acetone-d_6): δ 14.9 (CH_3), 19.9 (C-4), 25.0 (C-5), 29.7 (C-3), 30.5 (CH_2), 30.6 (*C*H_2COO), 60.9 (C-6), 61.1 (CH_2OR), 62.8 (C-1), 69.6 (C-2), 173.9 (C=O); IR (film): 3460, 2940, 2908, 2866, 1734, 1421, 1403, 1274 cm^{-1}; MS (EI), *m*/*z* (%): 214 (18) $[M]^+$, 196 (34), 164 (45), 126 (100); HRMS (EI): calcd for $C_{11}H_{18}O_4$ 214.120302, found 214.120344.

4.3. General procedure 2 for the Ti(IV) directed epoxide opening

A 0.5 M solution of the epoxide in dry CH_2Cl_2 was treated with Ti(O*i*Pr)$_4$ (1.3 equiv.) at room temperature and the resulting yellow solution stirred for 5 min at 25°C, before the nucleophile (1.4 equiv.), dissolved in dry CH_2Cl_2 (0.7 mL/mmol), was slowly added. Stirring was continued for 14 h, then the reaction was diluted with diethyl ether

(2 mL/mmol) and quenched with a 0.3N acetic acid solution. The mixture was neutralized with satd. $NaHCO_3$ solution, the phases were separated and the organic layer washed twice with water and brine (1 mL/mmol). Drying ($MgSO_4$), filtation, and concentration in vacuo gave the crude product.

4.3.1. *rel* Isopropyl 3-[(2*S*,6*S*)-1,2,6-trihydroxycyclohexyl]propanoate (13). According to general procedure 2, the epoxide **12** (2.0 g, 9.33 mmol) was reacted with propionic acid as nucleophile. Purification of the crude product by flash chromatography (petroleum ether/diethyl ether, 1:5) provided 1.26 g (55%) of **13** as white crystals, mp 71–72°C. TLC (hexane/diethyl ether, 1:5): R_f=0.23; ^{1}H NMR (acetone-d_6): δ 1.07 (d, J=6.3 Hz, 6H, 2×CH_3), 1.34–1.37 (m, 2H, CH_2), 1.48–1.49 (m, 3H, CH_2), 1.50–1.51 (m, 1H, CH_2), 1.87–1.93 (m, 2H, CH_2), 2.29–2.33 (m, 2H, CH_2), 3.53–3.55 (m, 1H, C*H*OH), 3.62–3.63 (m, 1H, C*H*OH), 4.80 (sep, J=6.3 Hz, 1H, $CHMe_2$); ^{13}C NMR (acetone-d_6): δ 19.5 (C-4), 22.5 (CH_3), 29.3 (C-3), 23.0 (C-5), 30.9 (CH_2), 31.2 (*C*H_2COO), 68.2 (O*C*H(CH_3)$_2$), 71.6 (C-6), 72.3 (C-2), 75.6 (C-1), 175.4 (COO); IR (KBr): 3437, 2941, 1711, 1436, 1249 cm^{-1}; MS (EI), *m*/*z* (%): 246 (8) $[M]^+$, 220 (12), 205 (30), 186 (34), 168 (100), 158 (42); HRMS (EI): calcd for $C_{12}H_{22}O_5$ 246.146038, found 246.146422.

4.3.2. *rel* Ethyl 3-[(1*S*,2*S*,6*S*)-2-(acetoxy)-1,6-dihydroxycyclohexyl]propanoate (14). Reaction of epoxide **12** (1.0 g, 4.67 mmol) with predried *n*Bu_4NOAc (for 10 min at 100°C in vacuo) according to general procedure 2 followed by flash chromatography (petroleum ether/diethyl ether, 1:5) of the crude product yielded 0.75 g (59%) of **14** as colorless crystalline solid, mp 54°C. TLC (hexane/diethyl ether, 1:5): R_f=0.35; ^{1}H NMR (acetone-d_6): δ 1.01 (t, J=7.1 Hz, 3H, CH_3), 1.32–1.37 (m, 3H, CH_2), 1.45–1.49 (m, 2H, CH_2), 1.55–1.70 (m, 2H, CH_2), 1.83 (s, 3H, CH_3), 1.88–1.89 (m, 1H, CH_2), 2.12–2.27 (m, 2H, CH_2), 3.46–3.47 (m, 1H, C*H*OH), 3.86 (q, 7.1 Hz, 2H, OCH_2), 4.72–4.74 (m, 1H, C*H*OR); ^{13}C NMR (acetone-d_6): δ=14.6 (CH_3), 19.2 (C-4), 21.2 (CH_3), 27.0 (C-5), 28.5 (C-3), 29.3 (CH_2), 30.3 (*C*H_2COO), 60.6 (CH_2OR), 72.3 (C-6), 74.1 (C-2), 85.6 (C-1), 170.5 (H_3C*C*O), 174.6 (CO); IR (KBr): 3528, 2936, 1730, 1701, 1374, 1248 cm^{-1}; MS (EI), *m*/*z* (%): 274 (7) $[M]^+$, 228 (16), 205 (4), 186 (20), 168 (100), 151 (30), 124 (80); HRMS (EI): calcd for $C_{13}H_{22}O_6$ 274.141206, found 274.141384.

4.3.3. *rel* Ethyl 3-[(3a*S*,4*S*,7a*S*)-4-(acetoxy)-2,2-dimethyltetrahydro-1,3-benzodioxol-3a(4*H*)-yl]propanoate (15). A solution of the diol **14** (0.7 g, 2.55 mmol), 2,2-dimethoxypropane (0.38 mL, 3.06 mmol, 1.2 equiv.), and a small amount of pyridinium *para* toluenesulfonic acid (PPTS) in dry acetone (10 mL) was stirred for 3 h at room temperature. The reaction was diluted with diethyl ether (30 mL) and washed twice with water (10 mL). The organic layer was dried over $MgSO_4$, filtered and concentrated in vacuo. Purification of the residue by flash chromatography (petroleum ether/diethyl ether, 1:2) gave 0.74 g (93%) of **15** as a colorless oil. TLC (hexane/diethyl ether, 1:4): R_f=0.83; ^{1}H NMR (C_6D_6): δ 1.09 (t, J=7.2 Hz, 3H, CH_3), 1.19–1.31 (m, 4H, CH_2), 1.32 (s, 3H, CH_3), 1.67 (s, 3H, CH_3), 1.78 (s, 3H, CH_3), 1.89–1.94 (m, 2H, CH_2), 2.48–2.63 (m, 4H, CH_2), 3.90–3.91 (m, 1H, C*H*OR), 4.04–4.13 (m, 2H, OCH_2), 5.47 (dd, J=11.9, 3.5 Hz, 1H, C*H*OR); ^{13}C NMR (C_6D_6): δ 12.9 (CH_3), 18.1 (C-6), 19.4 (H_3*C*CO), 22.4 (C-7), 24.2 (C-5), 25.5 (CH_3), 27.0 (CH_3), 27.3 (C-3), 27.8 (C-2), 58.9 (CH_2OR), 74.5 (C-7a), 76.2 (C-4), 80.7 (C-3a), 106.6 ((RO)$_2$*C*(CH_3)$_2$), 168.3 (*C*OCH_3), 172.0 (C-1); IR (film): 2942, 1726, 1694, 1354, 1246 cm^{-1}; MS (EI), *m*/*z* (%): 314 (10) $[M]^+$, 259 (8), 244 (67), 158 (100); HRMS (EI): calcd for $C_{16}H_{26}O_6$ 314.17226, found 314.17538.

4.3.4. *rel* (3a*R*,4*S*,7a*S*)-3a-(3-Hydroxypropyl)-2,2-dimethylhexahydro-1,3-benzodioxol-4-ol (16). Compound **15** (2.10 g, 6.66 mmol), dissolved in dry THF (25 mL) was slowly added to a suspension of $LiAlH_4$ (0.99 g, 26.70 mmol, 4 equiv.) in dry THF (15 mL) at 0°C. After complete addition, the cooling bath was removed and the mixture stirred for 4 h at room temperature. The reaction was quenched with water (25 mL) and the suspension extracted with ethyl acetate (3×35 mL). The combined organic phases were dried ($MgSO_4$), filtered, and concentrated in vacuo. Purification of the residue by flash chromatograpy with a gradient (diethylether→acetone) yielded diol **16** (1.16 g, 76%) as a gel. TLC (acetone/hexane, 2:3): R_f=0.25; ^{1}H NMR (acetone-d_6): δ 1.29 (s, 3H, CH_3), 1.42 (s, 3H, CH_3), 1.50–1.70 (m, 7H, CH_2), 1.95–2.15 (m, 3H, CH_2), 3.55–3.56 (m, 2H, CH_2OH), 3.81–3.83 (m, 1H, C*H*OR), 3.90–3.91 (m, 1H, CHOH); ^{13}C NMR (acetone-d_6): δ 20.3 (C-6), 25.0 (C-7), 26.9 (C-1), 27.7 (CH_3), 28.2 (C-2), 29.4 (CH_3), 31.9 (C-5), 63.7 (C-3), 75.1 (C-7a), 77.7 (C-4), 85.6 (C-3a), 107.8 ((RO)$_2$*C*(CH_3)$_2$); IR (KBr): 3451, 3382 (br, OH), 2955, 2914, 1234 cm^{-1}; MS (EI), *m*/*z* (%): 230 (8) $[M]^+$, 212 (14) $[M-H_2O]^+$, 188 (54), 154 (100); HRMS (EI): calcd for $C_{12}H_{22}O_4$ 230.15108, found 230.15244.

4.3.5. *rel* (3a*R*,4*S*,7a*S*)-3a-(3-{[*tert*-Butyl(dimethyl)silyl]-oxy}propyl)-2,2-dimethylhexahydro-1,3-benzodioxol-4-ol (17). A solution of the diol **16** (1.55 g, 6.73 mmol) in dry DMF (12 mL) was treated with TBDMSCl (1.1 g, 7.27 mmol, 1.08 equiv.) and DBU (1.41 mL, 9.42 mmol, 1.4 equiv.). The mixture was stirred for 24 h at room temperature, diluted with water (10 mL) and extracted with ethyl acetate (3×15 mL). After drying of the organic phase over $MgSO_4$, filtration, and concentration in vacuo, the residue was purified by flash chromatography (petroleum ether/diethyl ether, 4:6) to provide 1.81 g (88%) of **17** as a colorless oil. TLC (hexane/diethyl ether, 3:2): R_f=0.33; ^{1}H NMR (acetone-d_6): δ 0.00 (s, 6H, Si(CH_3)$_2$), 0.84 (s, 9H, C(CH_3)$_3$), 1.23 (s, 3H, CH_3), 1.35 (s, 3H, CH_3), 1.45–1.53 (m, 4H, CH_2), 1.61–1.64 (m, 2H, CH_2), 1.89–1.93 (m, 2H, CH_2), 1.99–2.00 (m, 1H, CH_2), 3.55–3.64 (m, 2H, CH_2OR), 3.76–3.77 (m, 1H, CHOR), 4.01–4.02 (m, 1H, C*H*OH); ^{13}C NMR (acetone-d_6): δ −4.6 (Si(CH_3)$_2$), 19.2 (*C*(CH_3)$_3$), 20.3 (C-6), 24.9 (C-7), 26.8 (C(*C*H_3)$_3$), 26.97 (C-1), 27.70 (CH_3), 28.31 (C-2), 29.40 (CH_3), 31.94 (C-5), 64.88 (C-3), 74.95 (C-7a), 77.73 (C-4), 85.52 (C-3a), 107.74 ((RO)$_2$*C*(CH_3)$_2$); IR (film): 3478, 2935, 2858, 1471, 1380, 1252, 1100, 889, 836 cm^{-1}; MS (FD), *m*/*z* (%): 344.9 (100) $[M]^+$.

4.3.6. *rel* (3a*S*,7a*S*)-3a-(3-{[*tert*-Butyl(dimethyl)silyl]-oxy}propyl)-2,2-dimethyltetrahydro-1,3-benzodioxol-4(3a*H*)-one (18). To a solution of alcohol **17** (1.8 g,

5.22 mmol) in dry CH_2Cl_2 (15 mL) was added dry pyridine (1.64 mL, 20.9 mmol, 4 equiv.) followed by the slow addition of Dess–Martin periodinane (DMP) (3.32 g, 7.83 mmol, 1.5 equiv.). After being stirred for 4 h at room temperature, the brownish solution was diluted with diethyl ether (15 mL) resulting in a brown precipitate. The solution was filtered and the filtrate washed thoroughly with a mixture of a freshly prepared satd. $Na_2S_2O_3$ and $NaHCO_3$ solution (1:1 v/v, 20 mL) and brine (10 mL). The organic layer was dried over $MgSO_4$, filtered, diluted with toluene (10 mL) and concentrated in vacuo giving a yellow oil. Purification of the residue by flash chromatography (petroleum ether/diethyl ether, 4:1) gave 1.41 g (79%) of **18** as a yellow oil, which is not stable towards air or light and must be stored in a cooling box under nitrogen. TLC (hexane/diethyl ether, 3:2): R_f=0.38; ^{1}H NMR (C_6D_6): δ −0.01, −0.00 (2 s, 6H, $Si(CH_3)_2$), 0.93 (s, 9H, $C(CH_3)_3$), 1.27 (s, 3H, CH_3), 1.28–1.33 (m, 2H, CH_2), 1.45 (s, 3H, CH_3), 1.51–1.54 (m, 2H, CH_2), 1.67–1.71 (m, 2H, CH_2), 1.80–1.86 (m, 3H, CH_2), 2.17–2.20 (m, 1H, CH_2), 3.42 (t, J=4.7 Hz, 2H, CH_2OR), 3.86–3.88 (m, 1H, CHOR); ^{13}C NMR (C_6D_6): δ −6.57 ($Si(CH_3)_2$), 17.09 ($C(CH_3)_3$), 19.75 (C-6), 24.76 ($C(CH_3)_3$), 24.88 (C-2), 25.79 (CH_3), 26.06 (CH_3), 26.32 (C-7), 28.75 (C-1), 38.91 (C-5), 61.58 (C-3), 80.19 (C-7a), 85.44 (C-3a), 106.91 ($(RO)_2C(CH_3)_2$), 207.37 (C-4); IR (film): 2953, 2935, 1726, 1472, 1380, 1248, 1101 cm^{-1}; MS (FD), m/z (%): 342.3 (100) $[M]^+$.

4.3.7. *rel* (3a*S*,7a*S*)-3a-(3-{[*tert*-Butyl(dimethyl)silyl]-oxy}propyl)-2,2-dimethyl-7,7a-dihydro-1,3-benzodioxol-4(3a*H*)-one (19). A suspension of freshly prepared *meta* iodoxybenzoic acid (1.26 g, 4.78 mmol, 3.3 equiv.) and diphenyldiselenide (0.14 g, 0.44 mmol, 0.3 equiv.) in dry toluene (9 mL) was heated to reflux. After 10–15 min the suspension became colorless. The suspension was cooled to 80°C before alcohol **17** (0.5 g, 1.45 mmol), dissolved in 2 mL of dry toluene was added dropwise to the reaction mixture. Stirring was continued for 3 h at 120°C, then the mixture was cooled to 80°C, and further amount of *meta* iodoxybenzoic acid (0.19 g, 0.72 mmol, 0.5 equiv.) was added and the reaction was stirred for further 3 h at 120°C. After cooling to room temperature, the mixture was diluted with diethyl ether (20 mL) and washed with satd. $NaHCO_3$ solution (10 mL), water (10 mL) and brine. Drying over $MgSO_4$, filtration and evaporation of the solvent gave a yellow oil, which was purified by flash chromatography (petroleum ether/diethyl ether, 4:1) to yield 0.38 g (76%) of **19** as a yellow, sticky oil. TLC (hexane/diethyl ether, 3:2): R_f=0.44; ^{1}H NMR (C_6D_6): δ 0.00, −0.01 (2 s, 6H, $Si(CH_3)_3$), 0.93 (s, 9H, $C(CH_3)_3$), 1.27 (s, 3H, CH_3), 1.32 (s, 3H, CH_3), 1.59–1.62 (m, 2H, CH_2), 1.70–1.74 (m, 2H, CH_2), 2.00 (ddd, J=20.2, 2.3, 2.3 Hz, 1H, CH_2), 2.34 (dd, J=20.2, 4.6 Hz, 1H, CH_2), 3.42–3.43 (m, 2H, CH_2OR), 3.93 (d, J=4.6 Hz, 1H, CHOR), 5.90 (dd, J=11.9, 2.2 Hz, 1H, CHR_3), 5.95–5.98 (m, 1H, CHR_3); ^{13}C NMR (C_6D_6): δ −6.6 ($Si(CH_3)_2$), 17.1 ($C(CH_3)_3$), 24.7 ($C(CH_3)_3$), 24.9 (CH_3), 25.6 (C-2), 26.3 (CH_3), 26.5 (C-1), 28.6 (C-7), 61.9 (C-3), 76.0 (C-7a), 81.4 (C-3a), 106.5 ($(RO)_2C(CH_3)_2$), 126.9 (C-5), 142.5 (C-6), 197.1 (C-4); IR (film): 2984, 2895, 1685, 1472, 138, 1251, 1097, 835 cm^{-1}; MS (FD), m/z (%): 340.2 (100) $[M]^+$.

4.3.8. *rel* Ethyl 3-[5-(acetoxy)-6-oxocyclohex-1-en-1-yl]propanoate (20). In a flask, fitted with a Dean–Stark trap, dry benzene (130 mL) was heated to 110°C and $Mn(OAc)_3{\cdot}2H_2O$ (24.61 g, 91.8 mmol, 1.5 equiv.) was added in six portions every 20 min. Heating was continued for 2–3 h at this temperature, until no more water separated. The deep red suspension was cooled to room temperature and the Dean–Stark trap replaced by a reflux condenser. At this point a solution of cyclohexenone **10** (12.0 g, 61.2 mmol) in dry benzene (20 mL) was added and the mixture refluxed for 24 h. After cooling, the deep brown suspension was diluted with ethyl acetate (50 mL) and 1N HCl solution (40 mL). After 10 min of vigorous stirring, the mixture was neutralized with satd. $NaHCO_3$ solution, filtered from the brown solid, and the layers were separated. The dark red organic solution was washed with brine (3×30 mL), and dried over $MgSO_4$. After filtration and concentration of the filtrate, the residue was purified by flash chromatography (petroleum ether/diethyl ether, 1:1) to provide the acetate **20** (10.72 g, 69%) as a bright yellow oil. TLC (hexane/diethyl ether, 1:1): R_f=0.34; ^{1}H NMR ($CDCl_3$): δ 1.05 (t, J=7.7 Hz, 3H, CH_3), 1.86–1.95 (m, 1H, CH_2), 1.98 (s, 3H, CH_3), 2.05–2.09 (m, 1H, CH_2), 2.24–2.35 (m, 6H, CH_2), 3.92 (q, J=7.0 Hz, 2H, OCH_2), 5.12–5.17 (m, 1H, C*H*OR), 6.61–6.62 (m, 1H, CHR_3); ^{13}C NMR ($CDCl_3$): δ 14.5 (CH_3), 21.0 (C-4), 25.0 (C-3), 25.4 (CH_3), 28.8 (CH_2), 33.2 (CH_2COO), 60.5 (CH_2OR), 74.0 (C-5), 137.4 (C-2), 145.9 (C-1), 170.2 ($COCH_3$), 172.9 (*C*OOEt), 194.1 (C-6); IR (film): 1739, 1734, 1691, 1374, 1236, 1187, 1098, 1043 cm^{-1}; MS (EI), m/z (%): 239 (8) $[M-CH_3]^+$, 196 (53) $[M-OAc]^+$, 179 (4), 150 (100), 122 (34); HRMS (EI): calcd for $C_{11}H_{16}O_3$ 196.109124, found 196.109825 $[M-OAc]^+$.

4.3.9. *rel* Ethyl 3-[(5*R*,6*R*)-5-(acetoxy)-6-hydroxycyclohex-1-en-1-yl]propanoate (21). To a solution of ketone **20** (3.0 g, 11.79 mmol) in dry methanol (6 mL) was added $CeCl_3{\cdot}7H_2O$ (3.07 g, 8.25 mmol) in dry methanol (7 mL) at room temperature while stirring. After 5 min the yellow solution was cooled to −5°C and $NaBH_4$ (0.47 g, 12.38 mmol) was slowly added such that the temperature stayed between −5 and 5°C (15 min). The mixture was stirred for 1.5 h at −5°C and, after removing of the cooling bath, stirring was continued for 1 h. The white suspension was evaporated to dryness and the solid extracted with diethyl ether (3×10 mL). The combined organic extracts were washed with brine (10 mL), dried over $MgSO_4$, filtered, and concentrated in vacuo. The oily residue was purified by flash chromatography (petroleum ether/diethyl ether, 1:3) to yield 2.57 g (85%) of **21** as a colorless oil. TLC (hexane/diethyl ether, 1:3): R_f=0.3; ^{1}H NMR ($CDCl_3$): δ 1.16–1.20 (m, 3H, CH_3), 1.60–1.68 (m, 1H, CH_2), 1.80–1.94 (m, 1H, CH_2), 1.97 (s, 3H, CH_3), 2.00–2.15 (m, 2H, CH_2), 2.39–2.46 (m, 4H, CH_2), 4.02–4.08 (m, 3H, C*H*OH, OCH_2), 4.80 (dt, J=11.4, 3.4 Hz, 1H, C*H*OR), 5.51 (m, 1H, CHR_3); ^{13}C NMR ($CDCl_3$): δ 14.6 (CH_3), 21.6 (C-4), 22.0 (C-3), 24.3 (CH_3), 30.0 (CH_2), 33.4 (CH_2COO), 60.7 (CH_2OR), 67.5 (C-6), 73.5 (C-5), 126.0 (C-2), 136.3 (C-1), 170.9 (H_3CCO), 173.8 (COOEt); IR (film): 3437, 2981, 1734, 1666, 1375, 1182, 1035 cm^{-1}; MS (EI), m/z (%): 255 (10) $[M-H]^+$, 209 (11), 194 (23), 168 (25), 148 (100); HRMS (EI): calcd for $C_{13}H_{19}O_5$ 255.12308, found 255.12365.

4.3.10. *rel* Ethyl 3-[(1*S*,2*S*,3*R*,6*R*)-3-(acetoxy)-2-hydroxy-7-oxabicyclo[4.1.0]hept-1-yl]propanoate (22). According

to general procedure 1 the alkenol **21** (2.5 g, 9.75 mmol) was converted to the epoxide **22**. Purification was done by flash chromatography (petroleum ether/diethyl ether, 2:3) providing 1.91 g of **22** (72%) as a colorless oil. TLC (petroleum ether/ethyl acetate, 1:1): R_f=0.28; ^{1}H NMR ($CDCl_3$): δ 1.19 (t, J=7.1 Hz, 3H, CH_3), 1.36–1.37 (m, 1H, CH_2), 1.55–1.69 (m, 1H, CH_2), 1.89–1.95 (m, 2H, CH_2), 2.02 (s, 3H, CH_3), 2.04–2.16 (m, 2H, CH_2), 2.36–2.42 (m, 2H, CH_2), 3.15–3.16 (m, 1H, epoxide-H), 4.04–4.09 (m, 3H, C*H*OH, OCH_2), 4.49 (dt, J=12.3 Hz, 3.8 Hz, 1H, CHOR); ^{13}C NMR ($CDCl_3$): δ 13.1 (CH_3), 16.6 (C-5), 20.1 (C-4), 22.4 (CH_3), 28.0 (CH_2), 29.4 (*C*H_2COO), 59.4 (C-6), 59.6 (CH_2OR), 60.8 (C-1), 65.6 (C-2), 70.9 (C-3), 169.6 (H_3C*C*O), 171.8 (*C*OOEt); IR (film): 3497, 2939, 1734, 1730, 1371, 1246 cm^{-1}; MS (EI), *m*/*z* (%): 272 (7) $[M]^+$, 271 (8) $[M\text{-}H]^+$, 243 (20), 223 (13), 215 (15), 213 (5) $[M-OAc]^+$, 198 (67), 165 (100); HRMS (EI): calcd for $C_{13}H_{20}O_6$ 272.12502, found 272.12568.

4.3.11. *rel* (6*R*,10*R*)-6,10-Dihydroxy-1-oxaspiro[4.5]-decan-2-one (24). A solution of epoxide **12** (1.0 g, 4.67 mmol) in dry CH_2Cl_2 (4 mL) was treated with Ti(O*i*Pr)$_4$ (1.66 mL, 5.60 mmol, 1.2 equiv.) at room temperature. The mixture was stirred for 10 min, cooled to 0°C and then dry ethanol (1.5 mL) was added. After 5 min, the cooling bath was removed and the mixture was stirred for further 8 h at room temperature. The yellow solution was quenched with water (1 mL) and extracted with ethyl acetate (4×15 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated in vacuo to obtain a colorless oil, which was purified by flash chromatography (ethyl acetate/petroleum ether, 4:1) yielding 0.56 g (64%) of **24** as a colorless gel. TLC (ethyl acetate/hexane, 7:3): R_f=0.24; ^{1}H NMR ($CDCl_3$): δ 1.37–1.51 (m, 2H, CH_2), 1.73–1.83 (m, 4H, CH_2), 2.36–2.67 (m, 4H, CH_2), 3.84–3.85 (m, 1H, C*H*OH), 4.07–4.10 (m, 1H, C*H*OH); ^{13}C NMR ($CDCl_3$): δ 16.9 (C-8), 23.9 (C-4), 27.8 (C-7), 28.7 (C-9), 29.4 (C-3), 69.2 (C-6), 72.2 (C-10), 90.3 (C-5), 177.1 (C-2); IR (KBr): 3427, 2942, 1757, 1458, 1213, 1044 cm^{-1}; MS (EI), *m*/*z* (%): 187 (4) $[M+H]^+$, 168 (20) $[M-H_2O]^+$, 151 (14), 124 (100), 111 (40), 84 (58); HRMS (EI): calcd for $C_9H_{12}O_3$ $[M-H_2O]^+$ 168.078631, found 168.080179.

4.3.12. *rel* (5*R*,6*R*,10*R*)-6-Bromo-10-hydroxy-1-oxaspiro[4.5]decan-2-one (25). To a solution of epoxide **12** (3.51 g, 16.40 mmol) in dry CH_2Cl_2 (12 mL) was added Ti(O*i*Pr)$_4$ (5.11 mL, 17.18 mmol, 1.05 equiv.) at room temperature. The mixture was stirred for 10 min at 25°C, cooled to −5°C and very slowly, a solution of bromine (0.88 mL, 17.18 mmol, 1.05 equiv.) in dry CH_2Cl_2 (2 mL) was added dropwise in such manner that the yellow color of the bromine vanished immediately. After addition, the cooling bath was removed and the reaction mixture stirred for further 8 h at room temperature. The bright red solution was quenched with a aqueous L-tartaric acid solution (15 mL), diluted with diethyl ether (40 mL) and stirred for 5 min, until two clear phases were observed. The layers were separated and the aqueous layer was extracted with ethyl acetate (2×30 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated in vacuo. Purification of the residue by flash chromatography (petroleum ether/diethyl ether, 1:3) gave 2.77 g (68%) of **25** as white crystals, mp 119°C. TLC (hexane/diethyl ether, 1:3): R_f=0.22; ^{1}H NMR (acetone-d_6): δ 1.58–1.62 (m, 4H, CH_2), 1.78–1.81 (m, 1H, CH_2), 2.03–2.16 (m, 3H, CH_2), 2.38–2.57 (m, 2H, CH_2), 3.96–3.97 (m, 1H, C*H*OH), 4.48–4.50 (m, 1H, CHBr); ^{13}C NMR (acetone-d_6): δ 21.1 (C-8), 30.2 (C-4), 30.4 (C-9), 30.7 (C-3), 33.7 (C-7), 59.2 (C-6), 72.7 (C-10), 88.9 (C-5), 177.2 (C-2); IR (KBr): 3415, 2955, 2927, 2532, 1749, 1450, 1232 cm^{-1}; MS (EI), *m*/*z* (%): 250 (4) $[M]^+$, 248 (3) $[M]^+$, 169 (6) $[M-Br]^+$, 151 (55), 124 (32), 101 (67); MS (FD), *m*/*z* (%): 250.1 (100) $[M]^+$, 248.1 (100) $[M]^+$.

4.3.13. *rel* (5*R*,6*R*,10*R*)-6-Bromo-10-[(trimethylsilyl)-oxy]-1-oxaspiro[4.5]decan-2-one (26). A solution of **25** (0.7 g, 2.81 mmol) in dry CH_2Cl_2 (4 mL) was cooled to 0°C and treated with hexamethyldisilazane (0.7 mL, 3.37 mmol, 1.2 equiv.), TMSCl (0.4 mL, 3.09 mmol, 1.1 equiv.) and a small amount of 4-DMAP. After being stirred for 2 h at room temperature, the reaction was carefully quenched with ice cold, satd. $NaHCO_3$ solution at 0°C and extracted with diethyl ether (3×15 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by flash chromatography (petroleum ether/diethyl ether, 3:2) resulting in 0.83 g (92%) of **26** as a colorless gel. TLC (hexane/diethyl ether, 3:2): R_f=0.45; ^{1}H NMR ($CDCl_3$): δ −0.07, −0.00 (2 s, 9H, $Si(CH_3)_3$), 1.57–1.59 (m, 4H, CH_2), 1.73–1.77 (m, 1H, CH_2), 2.02–2.09 (m, 3H, CH_2), 2.40–2.52 (m, 2H, CH_2), 3.97–3.98 (m, 1H, CHOR), 4.23–4.24 (m, 1H, CHBr); ^{13}C NMR ($CDCl_3$): δ 0.0, 0.7 ($Si(CH_3)_3$), 19.3 (C-8), 29.8, 29.8, 29.9, 23.0 (C-3, C-4, C-7, C-9), 57.2 (C-6), 72.5 (C-10), 87.3 (C-5), 176.4 (C-2); IR (film): 2960, 2876, 1762, 1274, 1168 cm^{-1}; MS (FD), *m*/*z* (%): 321.4 (100) $[M]^+$; HRMS (FT-ICR): calcd for $[C_{12}H_{21}O_3BrSi+Na]^+$ 343.03355, found 343.03368; found 345.03162.

4.3.14. *rel* (5*R*,6*R*,10*R*)-6-Bromo-10-{[*tert*-butyl-(dimethyl)silyl]oxy}-1-oxaspiro[4.5]decan-2-one (27). To a solution of the lactone **25** (3.0 g, 12.3 mmol) in dry CH_2Cl_2 (10 mL) were added TBDMSOTf (0.35 mL, 1.5 mmol, 1.25 equiv.) and imidazole (0.17 g, 24.6 mmol, 2 equiv.) at 0°C. After 10 min of stirring, the cooling bath was removed and the mixture was stirred for further 3 h at 25°C. After addition of brine (4 mL) the mixture was extracted with diethyl ether (3×20 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated leaving a yellow oil, which was purified by flash chromatography (petroleum ether/diethyl ether, 8:3) which gave 3.75 g (84%) of **27** as fine needles, mp 139°C. TLC (hexane/diethyl ether, 4:1): R_f=0.24; ^{1}H NMR ($CDCl_3$): δ −0.03, −0.00 (2 s, 6H, $Si(CH_3)_2$), 0.77 (s, 9H, $C(CH_3)_3$), 1.53–1.65 (m, 4H, CH_2), 1.76–1.77 (m, 1H, CH_2), 2.10–2.11 (m, 1H, CH_2), 2.13–2.15 (m, 2H, CH_2), 2.48–2.53 (m, 2H, CH_2), 3.95–3.97 (m, 1H, CHOR), 4.31 (m, 1H, CHBr); ^{13}C NMR ($CDCl_3$): δ −6.7 ($Si(CH_3)_2$), 16.0 (*C*$(CH_3)_3$), 17.7 (C-8), 23.7 (C(*C*$H_3)_3$), 27.7 (C-4), 27.7 (C-9), 27.9 (C-3), 28.3 (C-7), 55.3 (C-6), 71.3 (C-10), 85.9 (C-5), 174.4 (C-2); IR (KBr): 2951, 2891, 1760, 1409, 1281 cm^{-1}; MS (FD), *m*/*z* (%): 306.7 $[M-t\text{Bu}]^+$, 304.7 $[M-t\text{Bu}]^+$.

4.4. General procedure 3 for HBr-elimination

A 0.3 M solution of the spirolactone in benzene was treated

with DBU (1.5 equiv.). The solution was heated at 80°C for 2 h, cooled to room temperature and diluted with a mixture of diethylether/water (1:1). The organic phase was separated and the aqueous layer extracted three times with diethyl ether. The combined organic layers were dried over $MgSO_4$, filtered, and concentrated in vacuo.

4.4.1. *rel* (5*S*,10*R*)-10-[(Trimethylsilyl)oxy]-1-oxaspiro[4.5]dec-6-en-2-one (28). Lactone **26** (0.5 g, 1.56 mmol) was converted to the alkene **28** according to the general procedure 3. Purification of the crude product by flash chromatography (petroleum ether/diethyl ether, 3:2) gave 0.23 g (62%) of **28** as a yellow oil. TLC (hexane/diethyl ether, 3:2): R_f=0.3; ^{1}H NMR ($CDCl_3$): δ −0.08, −0.00 (2 s, 9H, $Si(CH_3)_3$), 1.54–1.56 (m, 1H, CH_2), 1.75–2.11 (m, 5H, CH_2), 2.34–2.37 (m, 1H, CH_2), 2.49–2.56 (m, 1H, CH_2), 3.56–3.60 (m, 1H, C*H*OR), 5.39 (d, *J*=11.9 Hz, 1H, CHR_3), 5.79–5.80 (m, 1H, CHR_3); ^{13}C NMR ($CDCl_3$): δ −0.1, 0.7 ($Si(CH_3)_3$), 25.0 (C-8), 26.8 (C-9), 29.6 (C-4), 32.3 (C-3), 75.0 (C-10), 83.3 (C-5), 128.0 (C-6), 133.5 (C-7), 177.0 (C-2); IR (film): 3023, 2954, 1761, 1423, 1384, 1242 cm^{-1}; MS (FD), *m*/*z* (%): 240.2 (100) $[M]^+$.

4.4.2. *rel* (5*S*,10*R*)-10-{[*tert*-Butyl(dimethyl)silyl]oxy}-1-oxaspiro[4.5]dec-6-en-2-one (29). Starting from lactone **27** (3.0 g, 8.2 mmol), elimination according to general procedure 3 and purification of the crude product by flash chromatography (petroleum ether/diethyl ether, 6:4) gave 2.15 g (93%) of **29** as colorless oil with an unpleasant odour. The oil solidified at −20°C, colorless crystals, mp 51°C. TLC (hexane/diethyl ether, 3:2): R_f=0.39; ^{1}H NMR ($CDCl_3$): δ 0.00 (s, 6H, $Si(CH_3)_2$), 0.79 (s, 9H, $C(CH_3)_3$), 1.63–1.64 (m, 1H, CH_2), 1.78–1.95 (m, 1H, CH_2), 1.98–2.01 (m, 2H, CH_2), 2.12–2.18 (m, 2H, CH_2), 2.42–2.44 (m, 1H, CH_2), 2.55–2.58 (m, 1H, CH_2), 3.61–3.65 (m, 1H, CHOR), 5.44 (d, *J*=10.6 Hz, 1H, CHR_3), 5.83–5.86 (m, 1H, CHR_3); ^{13}C NMR ($CDCl_3$): δ −5.3 ($Si(CH_3)_3$), 16.9 ($C(CH_3)_3$), 24.2 ($C(CH_3)_3$), 24.7 (C-8), 26.3 (C-9), 28.8 (C-4), 31.3 (C-3), 74.3 (C-10), 82.8 (C-5), 127.4 (C-6), 132.5 (C-7), 176.2 (C-2); IR (KBr): 3025, 2934, 1765, 1461, 1250, 1226, 1180, 1106 cm^{-1}; MS (FD), *m*/*z* (%): 283.2 $[M]^+$.

4.5. General procedure 4 for the epoxidation of compounds 28, 29 and 34

A mixture of the alkene (0.5 M in dry $CHCl_3$) and $MgSO_4$ (0.4 g/mmol of alkene) was treated with *m*CPBA (4 equiv.) at 25°C. Stirring was continued for 8 h, then the mixture was cooled to 0°C and cyclohexene (3 mL/mmol) was added dropwise. The cooling bath was removed and the mixture stirred for 1.5 h at room temperature. The white suspension was diluted with diethylether (8 mL/mmol) and washed twice with satd. $NaHCO_3$ solution (8 mL/mmol). The aqueous phase was extracted with diethyl ether (5 mL/mmol). The combined etheral layers were dried over $MgSO_4$, filtered and concentrated in vacuo.

4.5.1. *rel* (1′*R*,2*S*,3′*R*,6′*R*)-3′-[(Trimethylsilyl)oxy]dihydro-5*H*-spiro[furan-2,2′-[7]oxabicyclo[4.1.0]heptan]-5-one (30). Conversion of lactone **28** (0.35 g, 1.46 mmol) to the epoxycyclohexane **30** was performed according to general procedure 4. Purification of the crude product by flash chromatography (petroleum ether/diethyl ether, 3:2) delivered 0.28 g (74%) of **30** as a colorless, sticky oil. TLC (hexane/diethyl ether, 3:2): R_f=0.2; ^{1}H NMR ($CDCl_3$): δ −0.05, −0.04 (2 s, 9H, $Si(CH_3)_3$), 1.64–1.75 (m, 1H, CH_2), 1.80–1.90 (m, 1H, CH_2), 1.93–2.05 (m, 1H, CH_2), 2.15–2.25 (m, 2H, CH_2), 2.44–2.53 (m, 3H, CH_2), 3.05 (d, *J*=4.1 Hz, 1H, epoxide-H), 3.15–3.17 (m, 1H, epoxide-H), 3.62–3.65 (m, 1H, CHOR); ^{13}C NMR ($CDCl_3$): δ 0.0, −0.8 ($Si(CH_3)_3$), 21.5 (C-3), 25.3 (C-4′), 28.6 (C-4), 29.6 (C-5′), 53.4 (C-1′), 58.4 (C-6′), 71.3 (C-6), 83.9 (C-2′), 176.7 (C-5); IR (film): 2979, 2937, 2864, 1759, 142, 1290 cm^{-1}; MS (FD), *m*/*z* (%): 256.2 (100) $[M]^+$.

4.5.2. *rel* (1′*R*,2*S*,3′*R*,6′*R*)-3′-{[*tert*-Butyl(dimethyl)-silyl]oxy}dihydro-5*H*-spiro[furan-2,2′-[7]oxabicyclo-[4.1.0]heptan]-5-one (31). Alkene **29** (1.2 g, 4.26 mmol) was converted to the epoxide **31** according to general procedure 4. Purification by flash chromatography (petroleum ether/diethyl ether, 6:4) gave 0.83 g (65%) of **31** as a colorless solid, mp 49°C. TLC (hexane/diethyl ether, 3:2): R_f=0.29; ^{1}H NMR ($CDCl_3$): δ 0.00, −0.02 (2 s, 6H, $Si(CH_3)_2$), 0.81–0.84 (s, 9H, $C(CH_3)_3$), 1.37–1.39 (m, 1H, CH_2), 1.70–1.73 (m, 1H, CH_2), 1.83–1.92 (m, 1H, CH_2), 2.01–2.11 (m, 1H, CH_2), 2.25–2.32 (m, 2H, CH_2), 2.52–2.60 (m, 2H, CH_2), 3.11 (d, *J*=3.5 Hz, 1H, epoxide-H), 3.22–3.23 (m, 1H, epoxide-H), 3.66–3.69 (m, 1H, CHOR); ^{13}C NMR ($CDCl_3$): δ −5.8, −5.6 ($Si(CH_3)_2$), 16.9 ($C(CH_3)_3$), 20.5 (C-3), 24.3 (C-4′), 24.6 ($C(CH_3)_3$), 27.7 (C-4), 28.4 (C-5′), 52.7 (C-1′), 57.5 (C-6′), 70.4 (C-6), 83.1 (C-2′), 175.8 (C-5); IR (KBr): 2952, 2927, 2884, 2856, 1764, 1472, 1294, 1252, 1196 cm^{-1}; MS (FD), *m*/*z* (%): 298.3 (100) $[M]^+$.

4.5.3. *rel* (3*S*,5*S*,10*R*)-3-Azido-10-{[*tert*-butyl(dimethyl)-silyl]oxy}-1-oxaspiro[4.5]dec-6-en-2-one (32). To a solution of diisopropylamine (0.13 mL, 1.77 mmol) in dry THF (5 mL) was added *n*BuLi (1.73 mmol, 0.98 equiv., 2.5 M in hexane) dropwise at −78°C. The mixture was stirred for 30 min at −78°C, before lactone **29** (0.5 g, 1.77 mmol), dissolved in dry THF (2 mL), was added dropwise. After 30 min at this temperature, a solution of trisylazide (0.71 g, 2.3 mmol, 1.3 equiv.) in dry THF (2 mL) was added dropwise to the enolate solution. Stirring was continued for 15 min, then the bright yellow solution was treated with glacial acetic acid (0.47 mL, 8.14 mmol, 4.6 equiv.) and the mixture was slowly warmed to room temperature and kept for 5 h at 25°C. The mixture was diluted with CH_2Cl_2 (20 mL) and washed with satd. $NaHCO_3$ solution (2×10 mL) and brine (10 mL). The organic layer was dried over $MgSO_4$, filtered and concentrated in vacuo. Purification by flash chromatography (hexane/diethyl ether, 4:1) gave 0.51 g (89%) of **32** as colorless needles, mp 101°C. TLC (hexane/diethyl ether, 4:1): R_f=0.44; ^{1}H NMR ($CDCl_3$): δ −0.02 (s, 6H, $Si(CH_3)_2$), 0.78 (s, 9H, $C(CH_3)_3$), 1.59–1.62 (m, 1H, CH_2), 1.75–1.84 (m, 2H, CH_2), 1.96–2.02 (m, 1H, CH_2), 2.14–2.15 (m, 1H, CH_2), 2.39–2.45 (m, 1H, CH_2), 3.58–3.62 (m, 1H, CHOR), 4.39 (t, *J*=8.2 Hz, 1H, CHN_3), 5.39 (d, *J*=11.5 Hz, 1H, CHR_3), 5.89–5.92 (m, 1H, CHR_3); ^{13}C NMR ($CDCl_3$): δ −4.2 (Si $(CH_3)_2$), −3.8 ($Si(CH_3)_2$), 18.3 ($C(CH_3)_3$), 25.8 (C-8), 26.1 ($C(CH_3)_3$), 27.3 (C-9), 40.2 (C-4), 58.8 (C-3), 75.6 (C-10), 82.7 (C-5), 127.9 (C-6), 135.8 (C-7), 173.8 (C-2); IR (KBr): 2927, 2856, 2106 (N_3),

1765, 1472, 1460, 1288, 1261, 1103 cm^{-1}; MS (FD), *m/z* (%): 323.4 $[M]^+$.

4.5.4. *rel* (3*S*,5*S*,10*R*)-3-Amino-10-{[*tert*-butyl(dimethyl)-silyl]oxy}-1-oxaspiro[4.5]dec-6-en-2-one (33). A solution of azide **20** (0.5 g, 1.54 mmol) in dry THF (3 mL) was treated with triphenylphosphine (0.81 g, 3.08 mmol, 2 equiv.) at 25°C. Stirring was continued until no more gas bubbles were observed and the yellow color of the solution vanished (after 45 min). Water (800 μL) was added and the solution stirred for 24 h at 45°C. Thereafter, Na_2SO_4 (0.2 g) was added and the suspension vigorously stirred for 5 min, and then diluted with ethyl acetate (30 mL). After filtration, the mixture was evaporated to dryness. Purification by flash chromatography (petroleum ether/ethyl acetate 1:1→ethyl acetate) yielded 0.37 g (81%) of amine **21** as a colorless solid, mp 155°C. TLC (hexane/ethyl acetate, 1:1): R_f=0.1; ^1H NMR ($CDCl_3$): δ −0.00 (s, 6H, $Si(CH_3)_2$), 0.78 (s, 9H, $C(CH_3)_3$), 1.57–1.61 (m, 1H, CH_2), 1.77–1.81 (m, 2H, CH_2), 1.91–2.01 (m, 1H, CH_2), 2.10–2.15 (m, 1H, CH_2), 2.47–2.53 (m, 1H, CH_2), 3.62–3.65 (m, 1H, CHOR), 3.83 (t, *J*=7.9 Hz, 1H, C*H*NH_2), 5.40 (d, *J*=9.7 Hz, 1H, CHR_3), 5.83–5.85 (m, 1H, CHR_3); ^{13}C NMR ($CDCl_3$): δ −5.7, −5.4 ($Si(CH_3)_2$), 16.8 ($C(CH_3)_3$), 24.2 (C-8), 24.7 ($C(CH_3)_3$), 26.1 (C-9), 41.9 (C-4), 51.1 (C-3), 74.0 (C-10), 78.0 (C-5), 127.6 (C-6), 133.2 (C-7), 178.3 (C-2); IR (KBr): 3034, 2931, 2859, 1761, 1459, 1302, 1271 cm^{-1}; MS (FD), *m/z* (%): 297.3 $[M]^+$.

4.5.5. (5*S*,10*R*)-10-Hydroxy-1-oxaspiro[4.5]dec-6-en-2-one (34). A solution of lactone **29** (0.5 g, 1.77 mmol) in dry THF (3.5 mL) was treated with a TBAF solution (1.77 mL, 1 M in THF) at room temperature. After stirring for 30 min at 25°C, the mixture was diluted with brine (7 mL) and extracted with ethyl acetate (30 mL). The organic layer was dried over $MgSO_4$, filtered, and concentrated in vacuo. Purification by flash chromatography (petroleum ether/diethyl ether, 1:2) yielded 0.27 g (90%) of **34** as a sticky, clear oil. TLC (hexane/diethyl ether, 3:2): R_f=0.13; ^1H NMR ($CDCl_3$): δ 1.77–1.81 (m, 2H, CH_2), 1.98–2.13 (m, 2H, CH_2), 2.19–2.22 (m, 1H, CH_2), 2.37–2.38 (m, 1H, CH_2), 2.53–2.55 (m, 1H, CH_2), 2.66–2.71 (m, 1H, CH_2), 3.59–3.63 (m, 1H, CHOH), 5.52 (d, *J*=9.8 Hz, 1H, CHR_3), 5.88–5.92 (m, 1H, CHR_3); ^{13}C NMR ($CDCl_3$): δ 23.7 (C-8), 26.1 (C-9), 28.4 (C-4), 30.5 (C-3), 72.1 (C-10), 83.4 (C-5), 126.5 (C-6), 132.4 (C-7), 176.8 (C-2); IR (film): 3029, 2944, 2852, 1763, 1260, 1177 cm^{-1}; MS (EI), *m/z* (%): 168 (15) $[M]^+$, 151 (9) $[M-H_2O]^+$, 139 (100), 129 (45), 105 (67); HRMS (EI): calcd for $C_9H_{12}O_3$ 168.078631, found 168.079532.

4.5.6. *rel* (1′*R*,2*R*,3′*R*,6′*R*)-3′-Hydroxydihydro-5*H*-spiro-[furan-2,2′-[7]oxabicyclo[4.1.0]heptan]-5-one (35). Alkene **34** (0.6 g, 3.56 mmol) was converted to the epoxide **35** according to the general procedure 4. Flash chromatography (petroleum ether/diethyl ether, 1:9) gave 0.47 g (73%) of **35** as a colorless solid, mp 70–71°C. TLC (petroleum ether/diethyl ether, 1:9): R_f=0.33; ^1H NMR ($CDCl_3$): δ 1.45–1.50 (m, 1H, CH_2), 1.69–1.87 (m, 1H, CH_2), 1.91–1.97 (m, 1H, CH_2), 2.10–2.25 (m, 1H, CH_2), 2.31–2.33 (m, 2H, CH_2), 2.59–2.64 (m, 2H, CH_2), 3.11 (d, *J*=3.6 Hz, 1H, epoxide-H), 3.26–3.28 (m, 1H, epoxide-H), 3.60–3.63 (m, 1H, CHOH); ^{13}C NMR ($CDCl_3$): δ 19.4 (C-3), 22.8 (C-4′), 27.4 (C-4), 27.4 (C-5′), 52.9 (C-1′), 56.2 (C-6′), 68.5 (C-3′), 83.1 (C-2′), 176.1 (C-5); IR (KBr): 3418, 2937, 1760, 1574, 1417, 1263 cm^{-1}; MS (EI), *m/z* (%): 185 (7) $[M+H]^+$, 167 (8) $[M+H-H_2O]^+$, 156 (72), 139, 127 (100); HRMS (EI): calcd for $C_9H_{13}O_4$ 185.081378, found 185.082732.

4.5.7. *rel* (1′*R*,2*S*,6′*R*)-Dihydro-3′*H*,5*H*-spiro[furan-2,2′-[7]oxabicyclo[4.1.0]heptane]-3′,5-dione (36). A suspension of diphenyldiselenide (0.19 g, 0.65 mmol) and *meta* iodoxybenzoic acid (0.86 g, 3.25 mmol) in dry toluene (5 mL) was heated for 10 min at 130°C until the yellow color had disappeared. The white suspension was cooled to 80°C and slowly treated with a solution of **35** (0.4 g, 2.17 mmol) in dry toluene (3 mL). The mixture was stirred for 1.5 h at 80°C, cooled to room temperature and diluted with diethyl ether (30 mL). The yellow suspension was washed half saturated $NaHCO_3$ solution (2×10 mL) and brine (10 mL). After drying of the organic layer with $MgSO_4$, filtration and evaporation of the solvent in vacuo, the residue was purified by flash chromatography (petroleum ether/diethyl ether, 2:3) to yield 0.35 g (89%) of **36** as a colorless gel. TLC (hexane/diethyl ether, 2:3): R_f=0.2; ^1H NMR ($CDCl_3$): δ 2.27–2.32 (m, 4H, CH_2), 2.45–2.60 (m, 4H, CH_2), 3.30–3.31 (m, 1H, epoxide-H), 3.45 (d, *J*=2.7 Hz, 1H, epoxide-H); ^{13}C NMR ($CDCl_3$): δ 21.8 (C-3), 26.1 (C-4′), 27.3 (C-4), 30.3 (C-5′), 51.9 (C-6′), 56.0 (C-1′), 81.4 (C-2′), 174.7 (C-5), 202.5 (C-3′); IR (KBr): 2962, 2924, 1786, 1718, 1420, 1261, 1098, 1021 cm^{-1}; MS (FD), *m/z* (%): 182.1 (100) $[M]^+$.

4.6. General procedure 5 for the acid induced epoxide cleavage

A solution of the epoxide (0.4 M in dry THF) was treated with glacial acetic acid (3 equiv.) and dry LiBr (2 equiv.) under nitrogen. After stirring for 5 h at room temperature, the yellow mixture was treated with water (2 mL/mmol) and extracted three times with diethyl ether (12 mL/mmol). The combined organic extracts were dried over $MgSO_4$, filtered and concentrated in vacuo.

4.6.1. *rel* (5*R*,6*S*,7*S*,10*R*)-7-Bromo-6,10-dihydroxy-1-oxaspiro[4.5]decan-2-one (37). Epoxide **35** (0.5 g, 2.71 mmol) was converted to **37** according to the general procedure 5. Flash chromatography (petroleum ether/diethyl ether, 1:9) of the crude product gave 0.63 g (89%) of **37** as colorless crystals, mp 215°C (decomposition). TLC (petroleum ether/diethyl ether, 1:9): R_f=0.19; ^1H NMR (methanol-d_4): δ 1.50–1.53 (m, 1H, CH_2), 1.64–1.68 (m, 2H, CH_2), 1.95–2.01 (m, 1H, CH_2), 2.20–2.24 (m, 2H, CH_2), 2.42–2.45 (m, 1H, CH_2), 2.59–2.62 (m, 1H, CH_2), 3.80–3.81 (m, 1H, CHOH), 3.89–3.90 (m, 1H, CHBr), 4.00 (d, *J*=12 Hz, 1H, CHOH); ^{13}C NMR (methanol-d_4): δ 27.3 (C-4), 30.3 (C-9), 31.9 (C-3), 32.2 (C-8), 56.3 (C-7), 75.1 (C-10), 77.3 (C-6), 93.2 (C-5), 180.8 (C-2); IR (KBr): 3408, 3278, 2954, 1743, 1458, 1419, 1249 cm^{-1}; MS (FD), *m/z* (%): 265.0 (100) $[M]^+$, 267.0 (100) $[M]^+$.

4.6.2. *rel* (5*S*,6*S*,7*S*,10*R*)-7-Bromo-10-{[*tert*-butyl-(dimethyl)silyl]oxy}-6-hydroxy-1-oxaspiro[4.5]decan-2-one (38). Epoxide **31** (0.5 g, 1.67 mmol) was converted to **38** according to general procedure 5. Purification by flash chromatography (hexane/diethyl ether, 1:1) delivered 0.55 g

(87%) of **38** as white needles, mp 201°C (from hexane). TLC (hexane/diethyl ether, 1:1): R_f=0.19; ^{1}H NMR ($CDCl_3$): δ −0.01, −0.07 (2 s, 6H, $Si(CH_3)_2$), 0.84 (s, 9H, $C(CH_3)_3$), 1.43–1.62 (m, 3H, CH_2), 2.01–2.07 (m, 1H, CH_2), 2.26–2.29 (m, 2H, CH_2), 2.32–2.44 (m, 1H, CH_2), 2.71–2.76 (m, 1H, CH_2), 3.79–3.80 (m, 1H, CHOR), 3.82–3.83 (m, 1H, CHBr), 4.15 (d, J=13.9 Hz, 1H, CHOH); ^{13}C NMR ($CDCl_3$): δ −6.2, −5.6 ($Si(CH_3)_2$), 17.1 ($C(CH_3)_3$), 24.3 (C-4), 24.7 ($C(CH_3)_3$), 28.3 (C-9), 28.5 (C-3), 28.8 (C-8), 53.7 (C-7), 73.0 (C-10), 74.5 (C-6), 88.3 (C-5), 175.7 (C-2); IR (KBr): 3431, 2954, 2928, 2855, 1757, 1460, 1260, 1103, 1021, 926 cm^{-1}; MS (FD), *m/z* (%): 379.0 $[M]^+$, 381.0 $[M]^+$.

4.6.3. *rel* (5*S*,6*R*,7*S*,10*R*)-10-{[*tert*-Butyl(dimethyl)silyl]-oxy}-6-hydroxy-7-methoxy-1-oxaspiro[4.5]decan-2-one (39). To a solution of lactone **31** (1.0 g, 3.35 mmol) in dry methanol (15 mL) were added 2 drops of concentrated H_2SO_4. The mixture was stirred for 3 h at room temperature, neutralized with satd. $NaHCO_3$ solution, then most of the solvents were removed in vacuo. The residue was redissolved in diethyl ether (30 mL), the suspension filtered, and the ether layer dried over $MgSO_4$, filtered, and concentrated in vacuo. Purification by flash chromatography (petroleum ether/ethyl acetate, 1:1) yielded 0.9 g (81%) of **39** as colorless crystals, mp 132–133°C. TLC (hexane/ethyl acetate, 1:1): R_f=0.3; ^{1}H NMR ($CDCl_3$): δ 0.00, −0.07 (2 s, 6H, $Si(CH_3)_2$), 0.84 (s, 9H, $C(CH_3)_3$), 1.36–1.38 (m, 1H, CH_2), 1.55–1.69 (m, 3H, CH_2), 1.84–1.86 (m, 1H, CH_2), 2.31–2.42 (m, 2H, CH_2), 2.72–2.73 (m, 1H, CH_2), 3.01–3.02 (m, 2H, CH_2, CHOR), 3.38 (s, 3H, OCH_3), 3.75–3.76 (m, 1H, CHOR), 3.98 (d, J=12.0 Hz, 1H, CHOH); ^{13}C NMR ($CDCl_3$): δ −6.2, −5.7 ($Si(CH_3)_2$), 17.1 ($C(CH_3)_3$), 21.1 (C-9), 24.7 ($C(CH_3)_3$), 25.0 (C-4), 25.5 (C-3), 28.9 (C-8), 56.0 (OCH_3), 72.8 (C-6), 73.1 (C-10), 80.5 (C-7), 88.8 (C-5), 176.0 (C-2); IR (KBr): 3391, 2953, 2857, 1769, 1471, 1252 cm^{-1}; MS (FD), *m/z* (%): 330.3 $[M]^+$.

4.6.4. *rel* (5*S*,6*S*,7*S*,10*R*)-7-Bromo-10-{[*tert*-butyl(dimethyl)silyl]oxy}-2-oxo-1-oxaspiro[4.5]dec-6-yl benzoate (40). A solution of lactone **27** (0.9 g, 2.37 mmol) in dry pyridine (10 mL) was treated with DMAP (29 mg, 0.24 mmol, 0.1 equiv.), cooled to 0°C and benzoyl chloride (0.3 mL, 2.6 mmol, 1.1 equiv.) was slowly added to the mixture. After being stirred for 26 h at room temperature, the mixture was diluted with half saturated $NaHCO_3$ solution and extracted with diethyl ether (3×30 mL). The combined etheral extracts were dried over $MgSO_4$, filtrated and concentrated in vacuo. The residue was purified by flash chromatography (hexane/diethyl ether, 1:1) to give 1.0 g (88%) of **31** as white crystals, mp 177°C. TLC (hexane/diethylether, 4:7): R_f=0.3; ^{1}H NMR ($CDCl_3$): δ 0.00, −0.11 (2 s, 6H, $Si(CH_3)_2$), 0.87 (s, 9H, $C(CH_3)_3$), 1.53–1.54 (m, 1H, CH_2), 1.69–1.76 (m, 2H, CH_2), 2.12–2.13 (m, 1H, CH_2), 2.37–2.44 (m, 3H, CH_2), 2.51–2.54 (m, 1H, CH_2), 3.85–3.86 (m, 1H, CHOR), 3.94–4.00 (m, 1H, CHBr), 5.90–5.92 (d, J=10.6 Hz, 1H, CHOR), 7.33–7.37 (m, 2H, aromatic H), 7.46–7.50 (m, 1H, aromatic H), 7.92–7.94 (m, 2H, aromatic H); ^{13}C NMR ($CDCl_3$): δ −6.2, −5.7 ($Si(CH_3)_3$), 17.1 ($C(CH_3)_3$), 24.6 (C-4), 24.7 ($C(CH_3)_3$), 27.9 (C-9), 28.4 (C-3), 28.5 (C-8), 47.6 (C-7), 72.9 (C-10), 74.5 (C-6), 87.4 (C-5), 127.6, 128.4, 128.7, 132.4, 163.5 (COO), 173.9 (C-2); IR (KBr): 2965, 2939, 2844, 1769, 1725, 1421, 1203 cm^{-1}; MS (FD), *m/z* (%): 426.9 $[M-t\text{Bu}]^+$, 424.9 $[M-t\text{Bu}]^+$.

4.6.5. *rel* (5*S*,6*R*,10*R*)-10-{[*tert*-Butyl(dimethyl)silyl]-oxy}-2-oxo-1-oxaspiro[4.5]dec-7-en-6-yl benzoate (41). To a solution of spiro lactone **40** (1.0 g, 2.07 mmol) in dry toluene (10 mL) was added *N*-ethyldiisopropylamine (Hünig's base) (0.43 mL, 2.48 mmol, 1.2 equiv.) and the mixture heated at 155°C under reflux for 2.5 h. The mixture was cooled to room temperature, diluted with diethyl ether (10 mL) and washed with diluted acetic acid (15 mL), satd. $NaHCO_3$ solution (20 mL) and brine (20 mL). The organic layer was dried over $MgSO_4$, filtrated, and concentrated under reduced pressure. Purification by flash chromatography (petroleum ether/diethyl ether, 1:1) gave 0.59 g (71%) of **41** as colorless gel, besides 0.12 g (12%) of starting material **40**. TLC (hexane/diethyl ether, 2:3): R_f=0.55; ^{1}H NMR ($CDCl_3$): δ 0.00, −0.09 (2 s, 6H, $Si(CH_3)_2$), 0.85 (s, 9H, $C(CH_3)_3$), 2.13–2.20 (m, 2H, CH_2), 2.34–2.35 (m, 2H, CH_2), 2.53–2.64 (m, 2H, CH_2), 4.03–4.06 (m, 1H, CHOR), 5.57 (d, J=2.2 Hz, 1H, CHOR), 5.71–5.74 (m, 1H, CHR_3), 5.81–5.84 (m, 1H, CHR_3), 7.38–7.41 (m, 2H, aromatic H), 7.51–7.54 (m, 1H, aromatic H), 7.90–7.92 (m, 2H, aromatic H); ^{13}C NMR ($CDCl_3$): δ −5.4, −5.7 ($Si(CH_3)_2$), 17.0 ($C(CH_3)_3$), 24.7 ($C(CH_3)_3$), 26.0 (C-4), 28.1 (C-9), 31.5 (C-3), 70.3 (C-10), 72.6 (C-6), 85.4 (C-5), 122.0 (C-7), 127.6, 128.5 (aromatic C), 128.6 (C-8), 128.7, 132.4 (aromatic C), 164.5 (COO), 175.5 (C-2); IR (KBr): 3043, 2956, 2928, 1784, 1722, 1601, 1471, 1451, 1262, 1106 cm^{-1}; MS (FD), *m/z* (%): 402.3 $[M]^+$.

4.6.6. *rel* (1′*R*,2*S*,2′*R*,4′*R*,6′*R*)-4′-{[*tert*-Butyl(dimethyl)-silyl]oxy}-5-oxodihydro-3*H*-spiro[furan-2,3′-[7]oxa-bicyclo[4.1.0]heptan]-2′-yl benzoate (42). To a suspension of spirolactone **41** (0.5 g, 1.24 mmol) and $MgSO_4$ (0.5 g) in dry $CHCl_3$ (5 mL) was added *m*CPBA (0.86 g, 4.96 mmol, 4 equiv.) in small portions at −5°C. After complete addition, the mixture was stirred for 6 h at 35°C, cooled to 0°C and slowly treated with cyclohexene (10 mL). After further stirring for 30 min at 25°C, most of the solvent was removed in vacuo and the residue resuspended in ethyl acetate (20 mL). This was washed with satd. $NaHCO_3$ solution (3×20 mL). The organic layer was dried over $MgSO_4$, filtrated and concentrated in vacuo. Purification by flash chromatography (petroleum ether/diethyl ether, 3:2) yielded 0.38 g (63%) of **42** as colorless needles, mp 124°C. TLC (hexane/diethyl ether, 1:1): R_f=0.42; ^{1}H NMR ($CDCl_3$): δ 0.00, 0.08 (2 s, 6H, $Si(CH_3)_3$), 0.85 (s, 9H, $C(CH_3)_3$), 1.97–1.98 (m, 1H, CH_2), 2.09–2.11 (m, 2H, CH_2), 2.22–2.23 (m, 1H, CH_2), 2.52–2.56 (m, 2H, CH_2), 3.31–3.32 (m, J=3.5 Hz, 1H, epoxide H), 3.57 (t, J=3.5 Hz, 1H, epoxide H), 3.89 (t, J=4.8 Hz, 1H, CHOR), 5.56 (d, J=3.3 Hz, 1H, CHOR), 7.38–7.42 (m, 2H, aromatic H), 7.51–7.55 (m, 1H, aromatic H), 7.94–7.97 (m, 2H, aromatic H); ^{13}C NMR ($CDCl_3$): δ −5.8, −5.7 ($Si(CH_3)_2$), 17.0 ($C(CH_3)_3$), 24.7 ($C(CH_3)_3$), 25.3 (C-3), 28.1 (C-5′), 29.8 (C-4), 51.6 (C-1′), 52.0 (C-6′), 70.7 (C-4′), 72.2 (C-2′), 85.8 (C-3′), 127.6, 128.3, 128.7, 132.5 (aromatic C), 164.65 (COO), 174.99 (C-5); IR (KBr): 3442, 2930, 2856, 1783, 1723, 1574, 1451, 1324, 1262, 1106 cm^{-1}; MS (FD), *m/z* (%): 418.3 $[M]^+$.

4.6.7. *rel* (5*S*,6*R*,7*S*,8*S*,10*R*)-8-Bromo-10-{[*tert*-butyl-(dimethyl)silyl]oxy}-7-hydroxy-2-oxo-1-oxaspiro[4.5]-dec-6-yl benzoate (43). A solution of spirolactone **42** (0.4 g, 0.95 mmol) in dry THF (4 mL) was treated with glacial acetic acid (0.16 mL, 2.85 mmol, 3 equiv.) and dry LiBr (0.25 g, 2.85 mmol, 3 equiv.) and stirred for 5 h at 35°C. The reaction was quenched with water (5 mL) and extracted with diethyl ether (3×25 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated in vacuo. The residue was purified by flash chromatography (petroleum ether/diethyl ether, 1:1) resulting in 0.35 g (74%) of **43** as colorless crystals, 235–240°C (decomposition). TLC (hexane/diethyl ether, 1:1): R_f=0.36; ^{1}H NMR ($CDCl_3$): δ 0.00, 0.10 (2 s, 6H, $Si(CH_3)_3$), 0.82 (s, 9H, $C(CH_3)_3$), 2.05–2.10 (m, 2H, CH_2), 2.35–2.39 (m, 2H, CH_2), 2.50–2.56 (m, 2H, CH_2), 3.88–3.91 (m, 1H, CHOH), 4.13–4.16 (m, 2H, CHBr, CHOR), 5.57 (d, J=1.8 Hz, 1H, CHOR), 7.41–7.45 (m, 2H, aromatic H), 7.55–7.59 (m, 1H, aromatic H), 7.92–7.96 (m, 2H, aromatic H); ^{13}C NMR ($CDCl_3$): δ −5.9, −5.2 ($Si(CH_3)_2$), 16.9 ($C(CH_3)_3$), 24.6 ($C(CH_3)_3$), 26.9 (C-4), 27.1 (C-3), 37.8 (C-9), 49.0 (C-8), 70.9 (C-7), 71.7 (C-10), 74.0 (C-6), 84.8 (C-5), 127.7, 127.7, 128.8, 132.8 (aromatic C), 164.6 (COO), 174.8 (C-2); IR (KBr): 3442, 2962, 1785, 1735, 1261 cm^{-1}; MS (FD), *m/z* (%): 499.6 (100) $[M]^+$.

References

1. Su, J. Y.; Zhong, Y. L.; Zeng, L. M. *J. Nat. Prod.* **1993**, *56*, 288.
2. Cimanga, K.; Hermans, N.; Apers, S.; Van Miert, S.; Van den Heuvel, H.; Claeys, M.; Pieters, L.; Vlietinck, A. *J. Nat. Prod.* **2003**, *66*, 97–102.
3. (a) Paquette, L. A.; Bibart, R. T.; Seekamp, C. K.; Kahane, A. L. *Org. Lett.* **2001**, *3*, 4039–4041. (b) Paquette, L. A.; Owen, D. R.; Bibart, R. T.; Seekamp, C. K.; Kahane, A. L.; Lanter, J. C.; Corral, M. A. *J. Org. Chem.* **2001**, *66*, 2828–2834.
4. Michaut, M.; Santelli, M.; Parrain, J.-L. *Tetrahedron Lett.* **2003**, *44*, 2157–2159.
5. Taylor, S. K.; Chmiel, N. H.; Mann, E. E.; Silver, M. E.; Vyvyan, J. R. *Synthesis* **1998**, 1009–1014.
6. (a) Wipf, P.; Kim, Y.; Fritch, P. C. *J. Org. Chem.* **1993**, *58*, 7195–7203. (b) McKillop, A.; McLaren, L.; Taylor, R. J. K.; Watson, R. J.; Lewis, N. J. *J. Chem. Soc., Perkin Trans. 1* **1996**, 1385–1393. (c) Mukhopadhyay, T.; Bhat, R. G.; Roy, K.; Vijayakumar, E. K. S.; Ganguli, B. N. *J. Antibiot.* **1998**, *51*, 439–441.
7. Isolation: (a) Tanaka, M.; Nara, F.; Suzuki-Konagai, K.; Hosoya, T.; Ogita, T. *J. Am. Chem. Soc.* **1997**, *119*, 7871–7872. (b) Nara, F.; Tanaka, M.; Masuda-Inoue, S.; Yamasato, Y.; Doi-Yoshioka, H.; Suzuki-Konagai, K.; Kumakura, S.; Ogita, T. *J. Antibiot.* **1999**, *52*, 531–535.
8. Synthetic studies and analogs: (a) Izuhara, T.; Katoh, T. *Tetrahedron Lett.* **2000**, *41*, 7651–7655. (b) Saito, S.; Tanaka, N.; Fujimoto, K.; Kogen, H. *Org. Lett.* **2000**, *2*, 505–506. (c) Runcie, K. A.; Taylor, R. J. K. *Org. Lett.* **2001**, *3*, 3237–3239. (d) Hoye, T. R.; Tennakoon, M. A. *Org. Lett.* **2000**, *2*, 1481–1483. (e) Arenz, C.; Giannis, A. *Angew. Chem.* **2000**, *112*, 1498–1500, *Angew. Chem. Int. Ed.* **2000**, *39*, 1440–1442. (f) Fujioka, H.; Kotoku, N.; Sawama, Y.; Nagatomi, Y.; Kita, Y. *Tetrahedron Lett.* **2002**, *43*, 4825–4828. (g) Takagi, R.; Miyanaga, W.; Tamura, Y.; Ohkata, K. *Chem. Commun.* **2002**, 2096–2097. (h) Murray, L. M.; O'Brien, P.; Taylor, R. J. K. *Org. Lett.* **2003**, *5*, 1943–1946.
9. Drutu, I.; Njardarson, J. T.; Wood, J. L. *Org. Lett.* **2002**, *4*, 493–496.
10. Hwu, J. R.; Hakimelahi, G. H.; Chou, C.-T. *Tetrahedron Lett.* **1992**, *33*, 6469–6472.
11. (a) Stork, G.; Mook, R.; Biller, S. A.; Rychnovsky, S. D. *J. Am. Chem. Soc.* **1983**, *105*, 3741–3742. (b) Wu, H.-J.; Chao, C.-S.; Lin, C.-C. *J. Org. Chem.* **1998**, *63*, 7687–7693. (c) Danishefsky, S. J.; Myles, D. C.; Harvey, D. F. *J. Am. Chem. Soc.* **1987**, *109*, 862–867.
12. (a) Chong, J. M.; Sharpless, K. B. *J. Org. Chem.* **1985**, *50*, 1560–1563. (b) Alvarez, E.; Nuñez, M. T.; Martin, V. S. *J. Org. Chem.* **1990**, *55*, 3429–3431.
13. Barton, D. H. R.; Godfrey, C. R. A.; Morzycki, J. W.; Motherwell, W. B.; Ley, S. V. *J. Chem. Soc., Perkin Trans. 1* **1982**, 1947–1952.
14. Nicolaou, K. C.; Montagnon, T.; Baran, P. S.; Zhong, Y.-L. *J. Am. Chem. Soc.* **2002**, *124*, 2245–2258.
15. Dunlap, N. K.; Sabol, M. R.; Watt, D. S. *Tetrahedron Lett.* **1984**, *25*, 5839–5842.
16. Crystallographic data for the structures in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication numbers CCDC 216758 (**25**), CCDC 216759 (**37**). Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (Fax: +44(0)-1223-336033 or e-mail: deposit@ccdc.cam.ac.uk).
17. Evans, D. A.; Britton, T. C.; Ellman, J. A.; Dorow, R. L. *J. Am. Chem. Soc.* **1990**, *112*, 4011–4030.
18. Pellissier, H.; Michellys, P.-Y.; Santelli, M. *J. Org. Chem.* **1997**, *62*, 5588–5591.
19. de Sousa, S. E.; Kee, A.; O'Brien, P.; Watson, S. T. *Tetrahedron Lett.* **1999**, *40*, 387–390.
20. Hoveyda, A. H.; Evans, D. A.; Fu, G. C. *Chem. Rev.* **1993**, *93*, 1307–1370.
21. Sasaki, M.; Tanino, K.; Hirai, A.; Miyashita, M. *Org. Lett.* **2003**, *5*, 1789–1791, and references cited therein.
22. Chini, M.; Crotti, P.; Flippin, L. A.; Gardelli, C.; Macchia, F. *J. Org. Chem.* **1992**, *57*, 1713–1718.
23. Alvarez, E.; Nuñez, M. T.; Martin, V. S. *J. Org. Chem.* **1990**, *55*, 3429–3431.
24. Paruch, E.; Ciunik, Z.; Wawrzeńczyk, C.; Eur, *J. Org. Chem.* **1998**, 2677–2682.
25. Lochyński, S.; Frąckowiak, B.; Olejniczak, T.; Ciunik, Z.; Wawrzeńczyk, C. *Tetrahedron: Asymmetry* **2002**, *13*, 1761–1767.