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Enantioselective Preparation and Enzymatic Cleavage of Spiroisoxazoline Amides

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Dedicated to Professor Rolf Huisgen on the occasion of his 80th birthday

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Abstract—Several enantiopure spiroisoxazoline amides were prepared from *tert*-butylester **22**, which is obtained via an enantiotopic groups differentiating high pressure Diels–Alder cycloaddition. Treatment of these amides with an isoxazoline-splitting enzyme, which is involved in an injury induced defense reaction of the sponge *Aplysina cauliformis*, proves the bromoatoms in the cyclohexenone moiety to be important for enzyme binding, while the presence of the N–H bond of a monoalkylamide turned out to be mandatory for ring fission. The pertinence of these results to the ring splitting mechanism is discussed.

Introduction

The unusual spiroisoxazoline ring systems present in the agelorins (e.g. **1a**=agelorin A, Scheme 1) and the fistularins (e.g. **2**=11-*epi*-fistularin 3) which were isolated by König and Wright[1] from the Barrier Reef sponge *Agelas oroides* and which proved to be active against *Bacillus subtilis* and *Micrococcus luteus*[2] initiated synthetic work in various research groups.[3–7]

In our laboratory the pure enantiomers **9**–**14** were prepared from cycloadducts **7a** and **7b** which result from an enantiotopic double bonds differentiating high pressure Diels–Alder cycloaddition (Scheme 2).[8]

As communicated already,[9] these simple spiro compounds did easily match or even surpass the natural products in biological activity, but this comparison could easily become questionable in the light of the observation that the fistularins for instance are just at the starting point of an enzymatically catalyzed defense mechanism of sponges at least from the genus *Aplysina*,[10] which involves an isoxazoline splitting enzyme.

This enzymatic degradation of the fistularins and of related spiroisoxazoline amides gives rise to the β-hydroxynitrile aeroplysinine-1 **3** and to the dienone **4**, which obviously results from **3** via enolether hydrolysis and hydration of the nitrile group, and it were these metabolites that were proven to show remarkable antibiotic and cytotoxic activity.[11]

Starting from these results and having a reliable retro-Diels–Alder approach to key intermediates like **11** and **13** or their corresponding enantiomers at our disposal, we set out to prepare the relevant spiroamides. It was our aim to test the substrate specificity of the enzyme as well as the active site requirements and to elaborate the mechanism of the nitrile forming ring fission.

This could in principle be based either on nucleophilic attack at the carboxylic group (see **15**, Scheme 3) or on a deprotonation step at the N–H group of the amide (see **16**).

Results and Discussion

Although the most simple looking pyridone catalyzed ester aminolysis[12] worked quite well with our general intermediate **17** and pyrrolidine or piperidine to provide the disubstituted amides **18a** and **18b** (Scheme 4), the same process proved to be extremly unreliable with the much more important (see **16**) primary amines like benzylamine and cyclohexylamine.

Since NMR data on crude reaction products in these cases indicated conjugate addition to the cyclohexenone moiety to compete with amide formation, we decided to switch from methylester **17** to the corresponding acid derivatives and to generate the desired amides along Staab's well established carbonyl-diimidazole route.[13]

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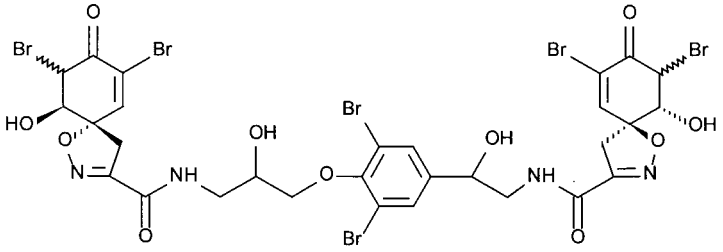
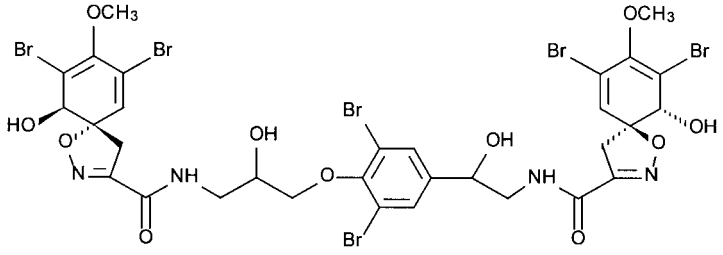
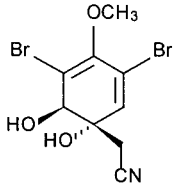


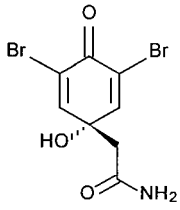
trans-bromohydrin: Agelorin A **1a**
cis-bromohydrin: Agelorin B **1b**



11-*epi*-Fistularin-3 **2**



Aeroplysinin-1 **3**



Dienone **4**

Scheme 1.

This called for an investigation of acid and base catalyzed hydrolysis of the intermediates in question and while proton catalyzed acetal splitting worked very well to provide diols **13** and **19** all our efforts to achieve base catalyzed ester hydrolysis met with failure.

A possible way to solve this problem would be to start with a *tert*-butylester right from the beginning and to prepare ester **22** via our Diels–Alder-retro-diene sequence. We were well aware of the additional risks of course, that come along with this special ester group—particularly in the retro step—we noticed on the other hand with some curiosity, however, that in our previous enantiotopic group differentiations we never had employed a *tert*-butylester.

To fill this gap and to gather some experience with this functional group too, we prepared ester **20** (Scheme 5) and were pleased to arrive at the enantiopure adduct **21** in an uneventfully high yield cycloaddition process.

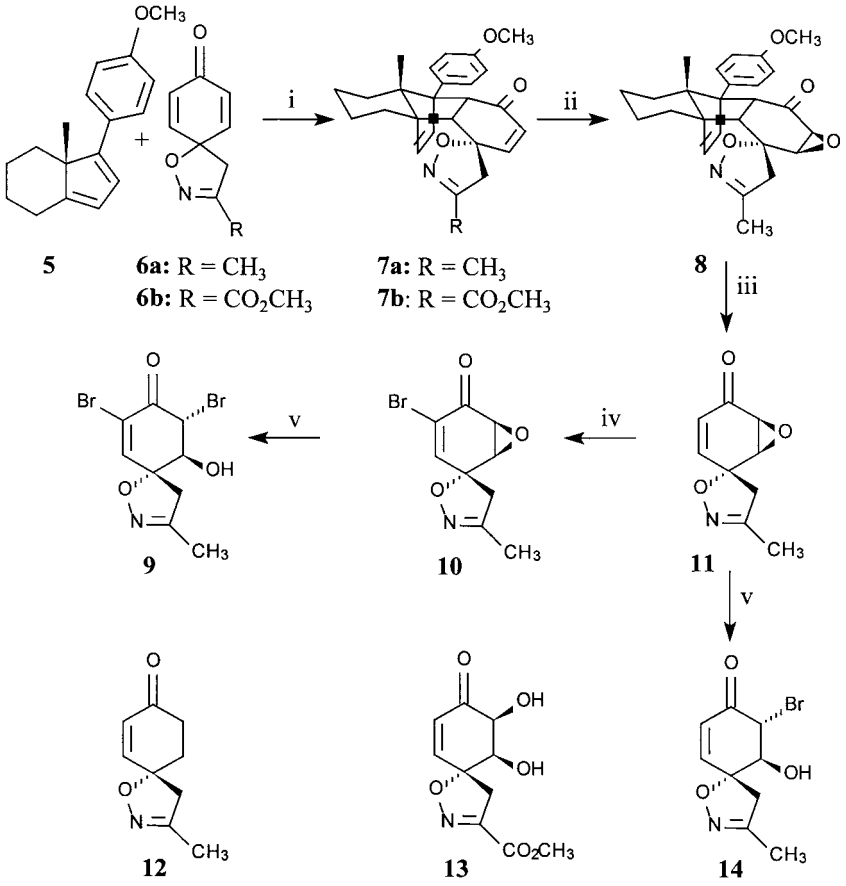
As expected hydroxylation[14] and diol protection with *p*-methoxy-benzaldehyde dimethylacetal operated nicely and even the retro-step could reliably be run with 50% yield, if the reaction flask was rinsed with triethylamine prior to the thermal process.

It should be mentioned at this stage, however, that the corresponding epoxide **26** although its preparation from **21** with *tert*-butylhydroperoxide and DBU[15] was achieved in 80% yield, gave only a disappointingly meager 13% of the retro-product **27** on thermolysis (Scheme 6).

This means that **27**, which is needed for regioselective and stereoselective introduction of the bromoatoms present in the natural products, would have to be synthesized from diol **24**.

Although the corresponding bromohydrin **28** looked like the most promising intermediate for this transformation, its preparation turned out to be by no means straightforward. A number of well-established methods for the bromination of alcohols, including the Appel technique[16] did either leave **13** unchanged or led to complete destruction of the molecule.

As preceding in situ formation of a tosylate at the hydroxy group to be substituted was considered an obvious way out of this dilemma we treated the esters **13** and **24** with tosyl chloride, Hünig's base and the triphenylphosphine–bromine complex in dichloromethane in the temperature range from 0°C to room temperature and were pleased to isolate 72% of the bromo epimers **14b** (Scheme 7) from methylester **13** and also 44% of the corresponding *tert*-butylester **28**.



Scheme 2. (i) 6.5 kbar, CH_2Cl_2, 21 d (**7a** 88%, **7b** 78%); (ii) KOH, H_2O_2, THF, 0°C (96%); (iii) 300°C, 10^{-2} mbar (83%); (iv) Br_2, Et_3N, CH_2Cl_2 (48%); (v) PPh_3Br_2, CH_2Cl_2, 0°C to rt (79%).

While on the first glance this seemed to confirm our assumption, a few disturbing observations made in the sequel cast serious doubt on the tosylate intermediate. First of all to be successful one had very much to stick to just one special mode of addition. It had to be treatment of triphenylphosphine with bromine in dichloromethane at 0°C first, after 5 min the Hünig's base had to be added, followed by a substoichiometric amount of tosyl chloride. Finally and still at 0°C one had to drop in the corresponding alcohol.

Since this sequence rather speaks against preformation of a tosylate, we checked the reaction with the independently prepared *tert*-butyl-cyclohexyl-*p*-toluenetosylate **33**,[17] to find that it was absolutely stable under reaction conditions, that led to quick bromination of the free alcohol.

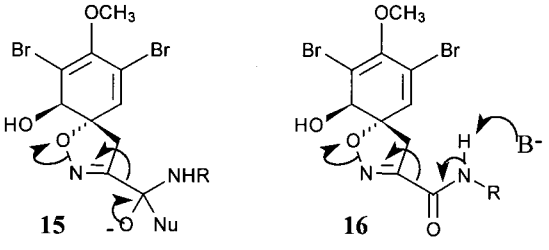
As bromohydrine formation in this cyclohexenone series additionally led to mixtures of epimers, which is not surprising in the presence of base, we first of all, using the procedure described above, prepared the configurational stable bromides **34**, **35a** and **35b** (Scheme 8) from the conformational rigid secondary alcohols menthol, androsterone and 3-*epi*-androsterone, which proved the bromination to be a clean inversion process, accompanied by the formation of triphenylphosphine oxide.

As far as the stereochemical outcome goes this indicates that one deals with a special route to the well-known Mitsunobu intermediate and although this still leaves open questions on details of this substitution reaction it turned out to be the only way to make the bromohydrins **14b** and **28** which on base treatment led to the epoxides **30a** and **27** as expected.

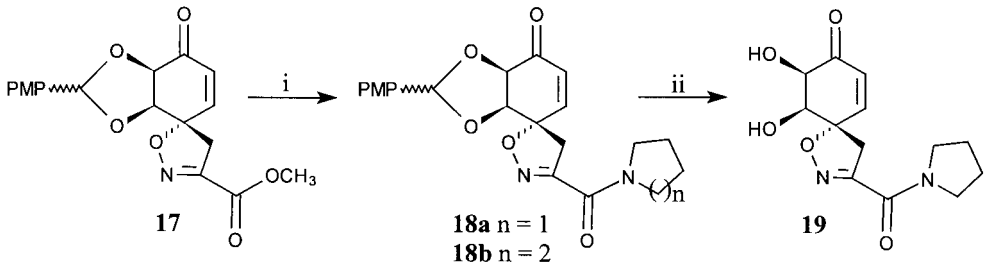
A very high yield Johnson bromination[18] followed by the again quantitative splitting of the *tert*-butylester provided acid **29c**, ready for amide formation.

Using benzylamine under Staab's conditions cleanly led to amide **31** which on epoxide opening[19] provided dibromoamide **32** having the agelorin type substitution pattern.

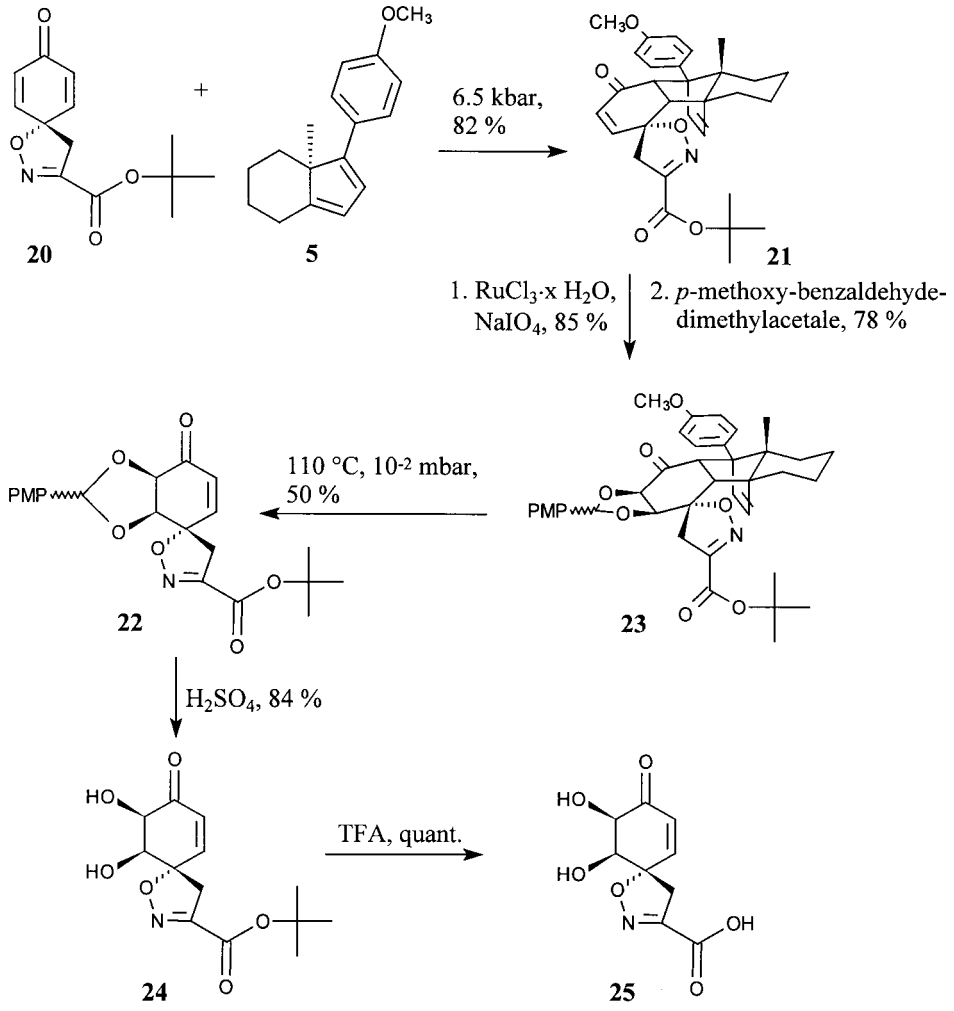
To have a comparable dibromomethylester available as a testsubstrate for the enzymatic ring fission (nucleophilic attack, see **15**) we started from acetal **17** described earlier and prepared bromodiol **36** again using Johnson's protocol, followed by acid catalyzed acetal hydrolysis (Scheme 9).



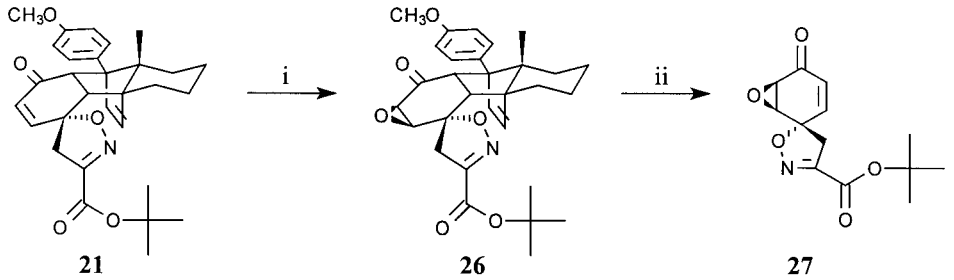
Scheme 3.



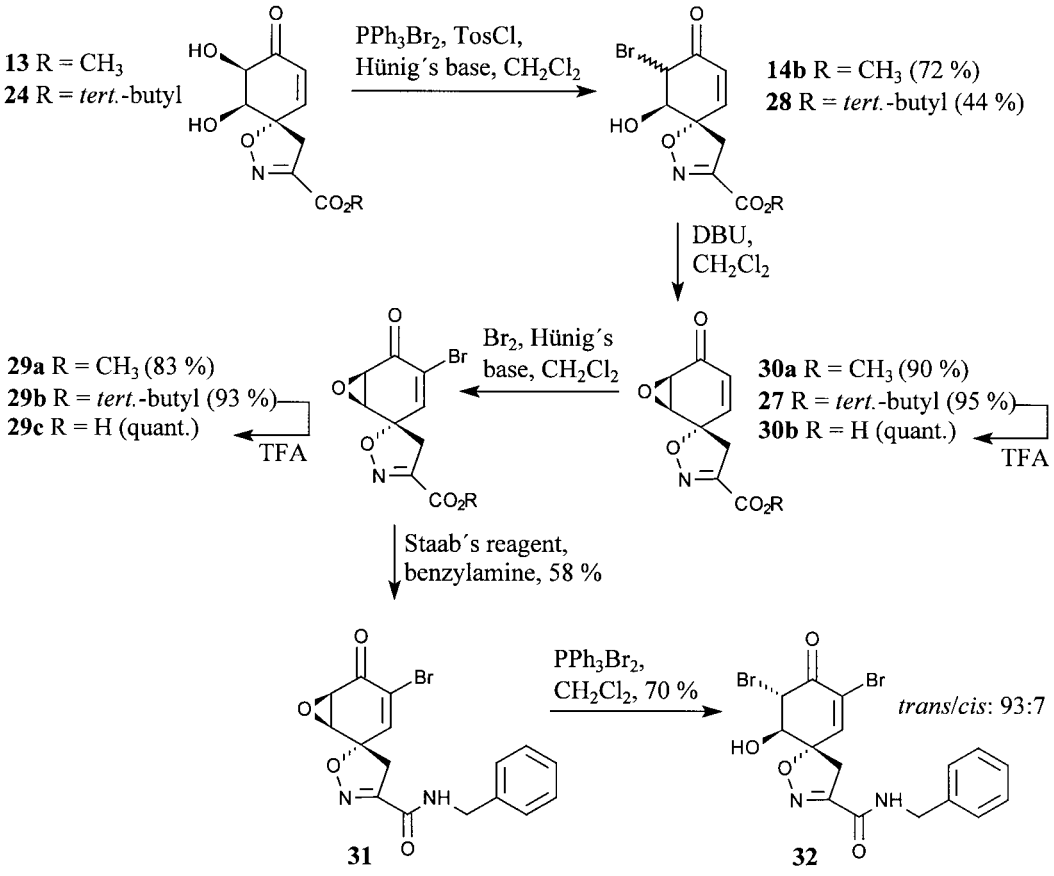
Scheme 4. (i) α-Pyridone, dioxane, rt, 10 min (**18a** 75%, **18b** 48%); (ii) H_2SO_4, acetone, rt, 30 min (74%).



Scheme 5.



Scheme 6. (i) *tert*-butylhydroperoxide, DBU (80%); (ii) 300°C, 1.5×10^{-2} mbar (13%).



Scheme 7.

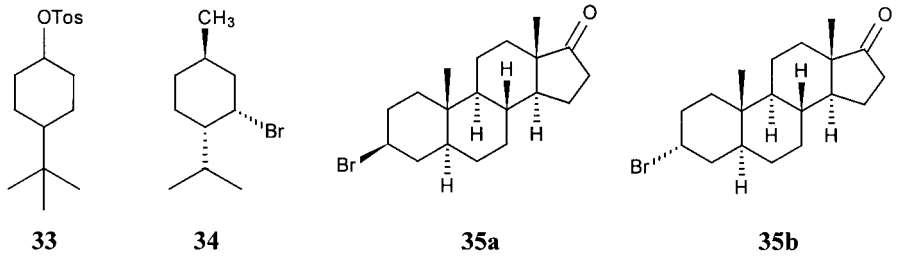
Bromination of this diol **36** under the conditions described above gave only a moderate yield of bromohydrin **38**, but since this compound is obtained in 96% yield from the corresponding epoxide **37**, this line was not investigated any further.

The Staab procedure did also work very satisfactorily with acid **25** to provide amide **39**. With acid **30b** we even succeeded in the preparation of bisamide **40**, which was, however, according to its polarity and low solubility not easily purified and had to be characterized by its IR- and MS-data along with some very characteristic NMR signals.

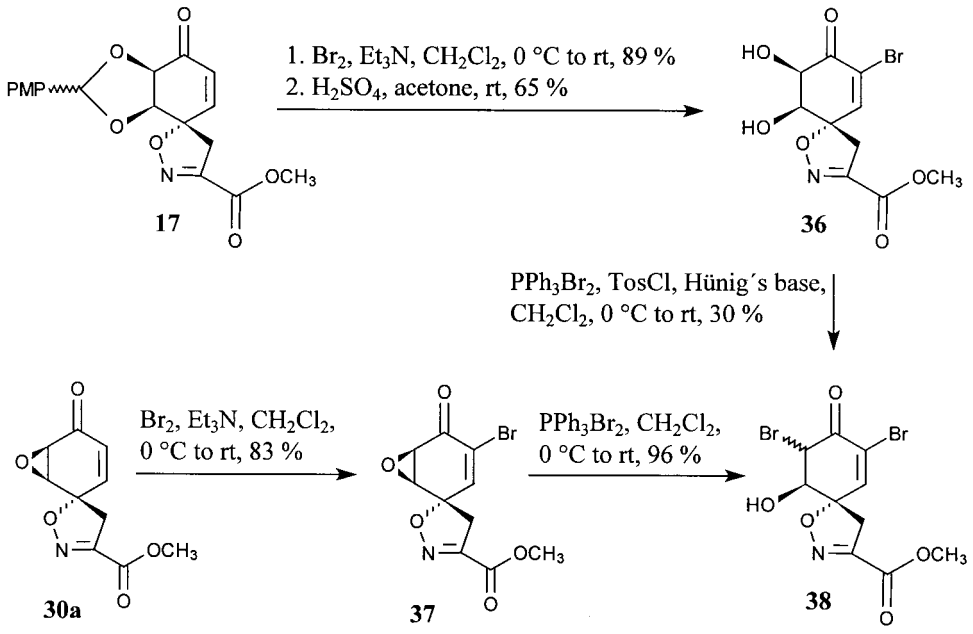
Having thus differently substituted brominated and not brominated amides as well as their ester analogues at our disposal we could start investigations with a cell free extract from *Aplysina cauliformis*, a sponge that had been collected in summer 1995 on Long Island (Bahamas) at a depth of 3 m.[10]

To check the general possibility to cleave spiroisoxazolines enzymatically,[20] numerous spiroisoxazoline derivatives were treated with the cell free extract, the most important ones were **19** (Scheme 4), **32** (Scheme 7), **38** (Scheme 9), **39** and **40** (Scheme 10).

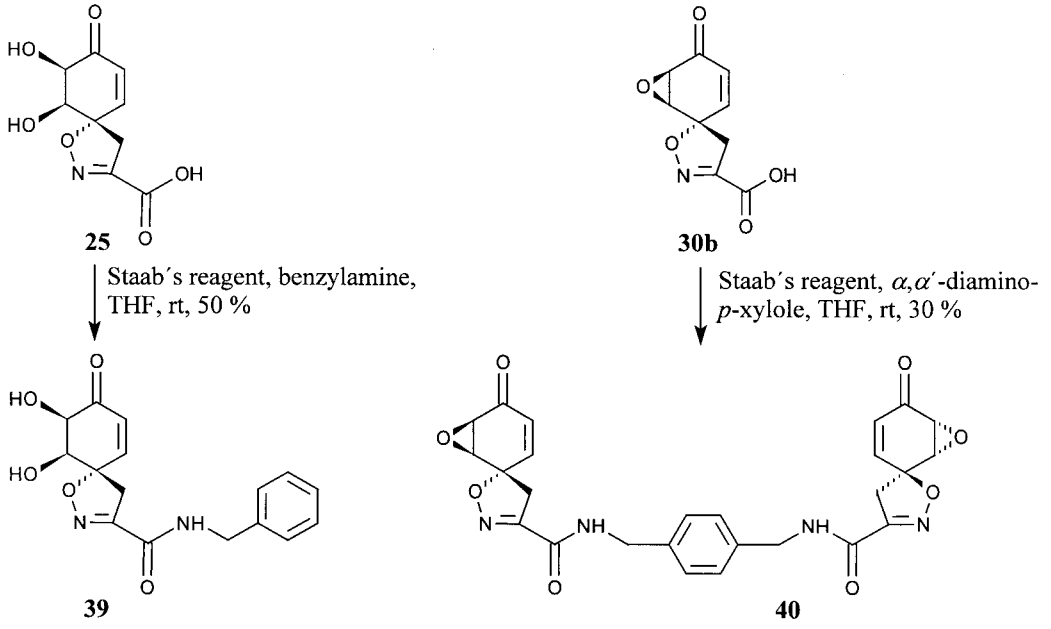
We observed that the non-brominated amides **19** and **40** as well as methylester **38** were not attacked by the enzyme at all, diolamide **39** was cleaved partly (30%) and dibromoamide **32** was split quantitatively. This result indicates the N–H bond, the hydroxy function and the two bromoatoms to play an important role for the enzymatic cleavage and points at cleaving mechanism **16** (Scheme 3).[23]



Scheme 8.



Scheme 9.



Scheme 10.

Because of its agelorin type substitution pattern in the cyclohexenone ring, bromohydrine **38** was additionally tested on its ability to inhibit competitively the active site of the enzyme against isofistularin.[23] However, dibromomethylester **38** showed no tendency to lower the enzyme activity, so that the N–H functionality seems to have some signification for the enzyme binding, too.

Our examinations demonstrate that the enzyme is highly specific and its only function is the ring fission reaction of the brominated spiroisoxazoline amides to form the toxic metabolite aeroplysinin-1 **3** (Scheme 1).

Experimental

General procedures

Melting points were determined on a Büchi melting point microscope and are uncorrected. UV spectra were measured on a Shimadzu 1601 instrument and IR spectra on a Perkin–Elmer 581 spectrometer. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker WP 200, Bruker AM 400 and Bruker AVS 400. δ_H Values are given relative to TMS=0; J values in Hz, δ_C values are given relative to $CDCl_3$=77.05; multiplicities of ^{13}C NMR were determined

by DEPT (90°/135°) or by APT. MS were determined with a Finnigan MAT 312 instrument and VG Autospec at 70 eV. Elemental analyses were recorded on a Heraeus CHN rapid analyzer. For flash chromatography silica gel (30–60 mesh; Baker) was used at 0.3 bar. The high pressure reactions were performed in a Hofer apparatus. For retro-Diels–Alder reactions a special flash vacuum pyrolysis apparatus was used. All solvents were dried by standard methods. Cyclopentadiene **5** was prepared according to the procedure described by Winterfeldt et al.,[21] spiroisoxazolines **6** and **20** were prepared as described.[22]

Experimental procedures

Protected pyrrolidineamide 18a. To a solution of acetal **17** (25 mg, 0.065 mmol) in dry dioxane (2 ml) were added α-pyridone (28 mg, 0.288 mmol, 4 equiv.) and afterwards pyrrolidine (35 mg, 0.478 mmol, 7 equiv.) at room temperature. After stirring the reaction mixture for 10 min it was quenched with water, extracted with ethyl acetate, dried ($MgSO_4$) and concentrated. Purification by flash chromatography yielded 21 mg (75%) of **18a** as a white foam; IR ($CHCl_3$): ν=2984 cm^{-1} (w), 2956 (m), 2928 (w), 1696 (m), 1628 (s), 1592 (m), 1452 (m), 1400 (m), 1264 (s), 1092 (m), 908 (s); ^1H NMR (400 MHz, $CDCl_3$): δ=1.86–2.02 (m, 4H, 11-H, 11′-H), 3.38 (d, *J*=18 Hz, 1H, 7-H), 3.55–3.62 (m, 2H, 10-H, 10′-H), 3.71–3.85 (m, 5H, 10-H, 10′-H, 17-H), 3.95 (d, *J*=18 Hz, 1H, 7-H), 4.58 (dd, *J*=2/6 Hz, 1H, 1-H), 4.64 (d, *J*=6 Hz, 1H, 2-H), 5.93 (s, 1H, 12-H), 6.28 (d, *J*=10 Hz, 1H, 4-H), 6.75 (dd, *J*=2/10 Hz, 1H, 5-H), 6.87 (d, *J*=9 Hz, 2H, 15-H, 15′-H), 7.27 (d, *J*=9 Hz, 2H, 14-H, 14′-H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=23.82 (C-11), 26.24 (C-11′), 45.08 (C-7), 47.14 (C-10), 48.75 (C-10′), 55.30 (C-17), 73.94 (C-1), 78.43 (C-2), 82.63 (C-6), 105.05 (C-12), 113.87 (C-15, C-15′), 127.72 (C-13), 128.24 (C-14, C-14′), 130.87 (C-4), 144.09 (C-5), 155.38 (C-16), 157.91 (C-8), 160.81 (C-9), 193.05 (C-3); MS (180°C): *m/z* (%)=399 (M+1, 1), 398 (M^+, 6), 371 (1), 300 (11), 245 (13), 152 (9), 137 (22), 135 (100), 122 (14), 98 (65), 92 (9), 77 (19), 70 (29); HRMS *m/z* for $C_{21}H_{22}N_2O_6$ calcd: 398.1478, found: 398.1478.

Protected piperidineamide 18b. To a solution of acetal **17** (20 mg, 0.056 mmol) in dry dioxane (2 ml) were added piperidine (70 mg, 0.882 mmol, 15 equiv.) and α-pyridone (20 mg, 0.206 mmol, 3.7 equiv.) at room temperature. After stirring the reaction mixture for 6 h it was quenched with water, extracted with ethyl acetate, dried ($MgSO_4$) and concentrated. Purification by flash chromatography yielded 11 mg (48%) of **18b** as a white foam; IR ($CHCl_3$): ν=3029 cm^{-1} (w), 2942 (m), 2860 (w), 1696 (m), 1630 (s), 1518 (m), 1480 (m), 1399 (w), 1254 (s), 1093 (m), 1002 (m); ^1H NMR (200 MHz, $CDCl_3$): δ=1.45–1.58 (m, 6H, 11-H, 11′-H, 12-H), 3.38 (d, *J*=18 Hz, 1H, 7-H), 3.58–3.97 (m, 8H, 10-H, 10′-H, 18-H, 7-H), 4.58–4.68 (m, 2H, 1-H, 2-H), 5.95 (s, 1H, 13-H), 6.28 (d, *J*=10 Hz, 1H, 4-H), 6.77 (dd, *J*=2/10 Hz, 1H, 5-H), 6.87 (d, *J*=9 Hz, 2H, 16-H, 16′-H), 7.29 (d, *J*=9 Hz, 2H, 15-H, 15′-H); MS (180 °C): *m/z* (%)=413 (M+1, 2), 412 (M^+, 9), 387 (21), 301 (25), 259 (26), 199 (3), 149 (9), 135 (79), 121 (13), 112 (100), 84 (59), 77 (16), 69 (43); HRMS: *m/z* for $C_{22}H_{24}N_2O_6$ calcd: 412.1634, found: 412.1635.

Diolepyrrolidineamide 19. To a solution of **18a** (21 mg, 0.053 mmol) in aq. acetone (3 ml) was added a catalytic amount of 2 N aq. H_2SO_4 at room temperature. After 30 min the reaction was stopped with $NaHCO_3$. The reaction mixture was concentrated and afterwards water was added. The aqueous phase was extracted with ethyl acetate. The combined organic layers were dried ($MgSO_4$) and concentrated. Chromatographic purification yielded 11 mg (74%) of **19** as a white foam; $[\alpha]_D^{20}$=79.5° (*c*=0.64, $CHCl_3$); IR ($CHCl_3$): ν=3496 cm^{-1} (w), 3400 (w), 3004 (m), 2980 (m), 2956 (w), 1700 (s), 1624 (s), 1596 (m), 1452 (m), 1380 (w), 1264 (s), 1112 (m), 908 (m); ^1H NMR (400 MHz, $CDCl_3$): δ=1.88–2.03 (m, symmetric, 4H, 11-H, 11′-H), 3.30 (d, *J*=18 Hz, 1H, 7-H), 3.50 (s, 1H, OH), 3.59 (tr, *J*=7 Hz, 2H, 10-H, 10′-H), 3.75–3.83 (m, 3H, 10-H, 10′-H, OH), 3.94 (d, *J*=18 Hz, 1H, 7-H), 4.21 (d_{br}, *J*=2 Hz, 1H, 1-H), 4.68 (d, *J*=2.5 Hz, 1H, 2-H), 6.23 (d, *J*=10 Hz, 1H, 4-H), 6.62 (d, *J*=2/10 Hz, 1H, 5-H); ^{13}C NMR (100 MHz, $CDCl_3$): ν=23.82 (C-11′), 26.23 (C-11), 44.86 (C-7), 47.21 (C-10′), 48.85 (C-10), 73.17 (C-1), 73.19 (C-2), 85.73 (C-6), 129.10 (C-4), 143.81 (C-5), 155.18 (C-8), 158.27 (C-9), 197.43 (C-3); MS (150°C): *m/z* (%)=281 (M+1, 2), 280 (M^+, 14), 251 (6), 220 (9), 193 (8), 149 (6), 139 (11), 136 (25), 135 (36), 125 (9), 98 (54), 86 (20), 70 (100); HRMS: *m/z* for $C_{13}H_{16}N_2O_5$ calcd: 280.1059, found: 280.1060.

Spiroisoxazoline adduct 21. A solution of diene **5** (2.66 g, 11.08 mmol) and spiroisoxazoline **20** (2.3 g, 9.24 mmol) in dichloromethane (7.5 ml) was introduced into a Teflon hose and submitted to 6.5 kbar in a high pressure autoclave for 14 days. Purification of the raw material by flash chromatography yielded 3.70 g (82%) of **21** as white foam; $[\alpha]_D^{20}$=123.6° (*c*=1.35, $CHCl_3$); IR ($CHCl_3$): ν=2984 cm^{-1} (m), 2934 (m), 2864 (m), 1711 (s), 1669 (s), 1637 (w), 1612 (m), 1593 (m), 1515 (s), 1443 (w), 1371 (m), 1252 (s), 1180 (m), 1140 (s), 910 (m); ^1H NMR (400 MHz, $CDCl_3$): δ=0.45 (d_{br}, *J*=13 Hz, 1H, 2-H_{eq}), 0.80 (s, 3H, 28-H), 1.06–1.64 (m, 5H), 1.57 (s, 9H, 20-H, 21-H, 22-H), 1.86 (dtr, *J*=3/13 Hz, 1H), 2.42 (dd, *J*=2.5/8.5 Hz, 1H), 2.86 (d, *J*=8 Hz, 1H, 11-H), 3.20 (d, *J*=18 Hz, 1H, 16-H), 3.26 (d, *J*=18 Hz, 1H, 16-H), 3.80–3.84 (m, 4H, 10-H, 27-H), 5.84 (d, *J*=10 Hz, 1H, 14-H), 5.88 (d, *J*=5.5 Hz, 1H, 7-H), 6.17 (d, *J*=5.5 Hz, 1H, 8-H), 6.51 (dd, *J*=1/10 Hz, 1H, 13-H), 6.87 (d, *J*=9 Hz, 2H, 25-H, 25′-H), 7.29 (d, *J*=9 Hz, 2H, 24-H, 24′-H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=15.40 (C-28), 21.13 (C-4), 23.81 (C-3), 27.13 (C-5), 28.03 (C-20, C-21, C-22), 28.57 (C-2), 50.26 (C-11), 51.67 (C-16), 51.68 (C-10), 55.17 (C-27), 61.31 (C-6), 62.36 (C-1), 70.87 (C-9), 83.84 (C-19), 87.66 (C-12), 113.10 (C-25, C-25′), 128.94 (C-23), 129.03 (C-24, C-24′), 130.99 (C-7), 135.62 (C-14), 138.62 (C-8), 147.29 (C-13), 151.64 (C-26), 158.31 (C-17), 159.38 (C-18), 198.09 (C-15); MS (80°C): *m/z* (%)=489 (M^+, 4), 372 (7), 371 (6), 305 (6), 240 (30), 234 (14), 211 (11), 210 (9), 193 (12), 176 (100), 153 (16), 119 (29); FAB-MS: *m/z* (%)=512 (M+23, 81), 490 (M+1, 100), 460 (25), 434 (94).

Spiroisoxazoline diol adduct. To a solution of **21** (4.30 g, 8.81 mmol) and CH_3CN (50 ml) and EtOAc (50 ml) was added with vigorous stirring a solution of $RuCl_3 \cdot xH_2O$ (461 mg, 2.23 mmol, 0.25 equiv.) and $NaIO_4$ (3.58 g,

16.73 mmol, 1.9 equiv.) in deionized water at 0°C. After 5 min the reaction mixture was quenched with sat. aq. $NaHSO_5$. The aqueous phase was extracted with ethyl acetate. The combined organic layers were dried ($MgSO_4$) and concentrated. Purification by flash chromatography yielded 3.92 g (85%) of the diol adduct as yellow foam; $[\alpha]_D^{20}$=74.9° (*c*=0.41, $CHCl_3$); IR ($CHCl_3$): ν=3587 cm^{-1} (w), 2985 (w), 2934 (w), 1710 (s), 1595 (w), 1516 (m), 1443 (w), 1371 (m), 1265 (s), 1127 (m), 1106 (m), 909 (m); ^1H NMR (400 MHz, $CDCl_3$): δ=0.51 (d_{br}, *J*=13 Hz, 1H, 2-H_{eq}), 0.79 (s, 3H, 28-H), 1.11–1.98 (m, 7H), 1.58 (s, 9H, 20-H, 21-H, 22-H), 2.94 (d, *J*=9 Hz, 1H, 11-H), 3.03 (d, *J*=18 Hz, 1H, 16-H), 3.72–3.94 (m, 6H, 27-H, 16-H, 10-H, 14-H), 4.18 (d, *J*=2 Hz, 1H, 13-H), 5.97 (d, *J*=6 Hz, 1H, 7-H), 6.45 (d, *J*=6 Hz, 1H, 8-H), 6.88 (d, *J*=9 Hz, 2H, 25-H, 25′-H), 7.28 (d, *J*=9 Hz, 2H, 24-H, 24′-H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=16.08 (C-28), 21.18 (C-4), 23.60 (C-3), 26.35 (C-5), 28.04 (C-20, C-21, C-22), 28.41 (C-2), 45,47 (C-16), 52.05 (C-10), 52.95 (C-11), 55.18 (C-27), 61.81 (C-6), 62.81 (C-1), 69.03 (C-9), 74.00 (C-13), 75.91 (C-14), 83.84 (C-19), 90.20 (C-12), 113.17 (C-25, C-25′), 128.87 (C-23), 128.94 (C-24, C-24′), 132.50 (C-7), 142.93 (C-8), 152.61 (C-29), 158.61 (C-17), 159.67 (C-18), 211.23 (C-15); FAB-MS: *m*/*z* (%)=546 (M+23, 100), 524 (M+1, 17), 523 (27), 508 (7), 495 (10), 490 (12).

Protected spiroisoxazoline adduct 23. To a solution of spiroisoxazoline diol adduct (4.06 g, 7.76 mmol) in dry CH_3CN (50 ml) were added *p*-methoxy-benzaldehyde acetal (4.00 g, 22.10 mmol, 2.8 equiv.) and a catalytic amount of *p*TsOH at 0°C. After 30 min at room temperature the reaction mixture was quenched with sat. aq. $NaHSO_3$. The aqueous phase was extracted with methyl *tert*-butyl ether. The combined layers were washed with brine and dried ($MgSO_4$). Evaporation of the solvent and purification by flash chromatography yielded 3.87 g (78%) of **23** as a white solid; melting point=80.7°C; IR ($CHCl_3$): ν=2935 cm^{-1} (m), 1714 (s), 1614 (m), 1594 (m), 1517 (s), 1463, 1441 (m), 1371 (m), 1252 (s), 1181 (m), 1171 (m), 1935 (m), 909 (m); ^1H NMR (200 MHz, $CDCl_3$): δ=0.62 (d_{br}, 1H, 2-H_{eq}), 0.79 (s, 3H, 34-H), 1.12–1.73 (m, 4H), 1.54 (s, 9H, 20-H, 21-H, 22-H), 1.95–2.14 (m, 3H), 3.20 (m, 2H, 11-H, 16-H), 3.54 (d, *J*=18 Hz, 1H, 16-H), 3.78 (s, 3H, 28-H), 3.83 (s, 3H, 33-H), 4.27 (d, *J*=8 Hz, 1H, 13-H), 4.29 (d, *J*=10 Hz, 1H, 10-H), 4.48 (d, *J*=8 Hz, 1H, 14-H), 5.79 (s, 1H, 23-H), 6.09 (d, *J*=6 Hz, 1H, 7-H), 6.23 (d, *J*=6 Hz, 1H, 8-H), 6.85 (d, *J*=9 Hz, 2H, 31-H, 31′-H), 6.96 (d, *J*=9 Hz, 2H, 26-H, 26′-H), 7.16 (d, *J*=9 Hz, 2H, 30-H, 30′-H), 7.45 (d, *J*=9 Hz, 2H, 25-H, 25′-H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=15.73 (C-34), 21.03 (C-4), 23.44 (C-3), 27.66 (C-5), 28.00 (C-20, C-21, C-22), 28.55 (C-2), 43.17 (C-16), 51.75 (C-11), 52.37 (C-10), 55.21 (C-28), 55.31 (C-33), 60.50 (C-6), 63.22 (C-1), 64.92 (C-9), 78.27 (C-13), 80.81 (C-14), 80.68 (C-19), 89.84 (C-12), 104.83 (C-23), 113.52 (C-31, C-31′), 114.09 (C-26, C-26′), 127.13 (C-24), 128.06 (C-30, C-31′), 128.09 (C-25, C-25′), 129.72 (C-29), 136.25 (C-7), 138.67 (C-8), 152.76 (C-32), 158.32 (C-27), 159.34 (C-17), 160.98 (C-18), 203.78 (C-15); FAB-MS: *m*/*z* (%)=664 (M+23, 25), 642 (M+1, 26), 586 (8), 540 (9), 402 (100), 391 (5), 368 (8), 346 (37), 329 (9), 307 (19), 289 (11).

Protected diol 22. A flask of a flash vacuum pyroysis apparatus was rinsed with triethylamine. Then adduct **23** (500 mg, 0.780 mmol) was brought into it and heated to 110°C at 10^{-2} mbar. This way the developed diene **5** was sublimed and **22** remained in the reaction flask. Chromatographic purification yielded 156 mg (50%) as a yellow solid; melting point=122.2°C; IR ($CHCl_3$): ν=2984 cm^{-1} (w), 2936 (w), 1714 (s), 1614 (m), 1597 (w), 1459 (w), 1371 (m), 1254 (s), 1173 (m), 1151 (m), 1126 (m), 830 (m); UV ($CHCl_3$): λ_{max}=261 nm; ^1H NMR (200 MHz, $CDCl_3$): δ=1.56 (s, 9H, 11-H, 12-H, 13-H), 3.21 (d, *J*=18 Hz, 1H, 7-H), 3.70–3.89 (m, 4H, 7-H, 19-H), 4.58–4.77 (m, 2H, 1-H, 2-H), 5.94 (s, 1H, 14-H), 6.27 (d, *J*=10 Hz, 1H, 4-H), 6.74 (dd, *J*=10/1.5 Hz, 1H, 5-H), 6.87 (d, *J*=9 Hz, 2H, 17-H, 17′-H), 7.28 (d, *J*=9 Hz, 2H, 16-H, 16′-H); ^{13}C NMR (50 MHz, $CDCl_3$): δ=27.98 (C-11, C-12, C-13), 43.11 (C-7), 55.31 (C-19), 73.91 (C-1), 78.40 (C-2), 84.24 (C-10), 84.63 (C-6), 105.05 (C-14), 113.90 (C-17, C-17′), 127.66 (C-15), 128.26 (C-16, C-16′), 130.83 (C-4), 143.65 (C-5), 153.09 (C-18), 158.75 (C-8), 166.86 (C-9), 192.80 (C-3); FAB-MS: *m*/*z* (%)=424 (M+23, 7), 402 (M+1, 34), 391 (7), 346 (14), 329 (18), 307 (29), 289 (20), 259 (26), 241 (12), 176 (35), 154 (100).

Spiroisoxazoline diol 24. To a solution of **22** (550 mg, 1.38 mmol) in aq. acetone (3 ml) was added a catalytic amount of 2 N aq. H_2SO_4 at room temperature. After 3 h the reaction was stopped with $NaHCO_3$. The reaction mixture was concentrated and afterwards water was added. The aqueous phase was extracted with ethyl acetate. The combined organic layers were dried ($MgSO_4$) and concentrated. Chromatographic purification yielded 327 mg (84%) of **24** as a white foam; $[\alpha]_D^{20}$=19.6° (*c*=0.14, MeOH); IR ($CHCl_3$): ν=3580 cm^{-1} (w), 3506 (w), 2984 (w), 1703 (s), 1597 (m), 1458 (w), 1371 (m), 1261 (m), 1127 (m), 909 (m); ^1H NMR (400 MHz, acetone-d_6): δ=1.53 (s, 9H, 11-H, 12-H, 13-H), 3.27 (d, *J*=18 Hz, 1H, 7-H), 3.73 (d, *J*=18 Hz, 1H, 7-H), 4.17 (m, 1H, 1-H), 4.40 (d, *J*=4 Hz, 1H, OH), 4.54 (tr_{br}, *J*=4 Hz, 1H, 2-H), 5.07 (d, *J*=4 Hz, 1H, OH), 6.14 (d, *J*=10 Hz, 1H, 4-H), 6.81 (d,*J*=10/2 Hz, 1H, 5-H); ^{13}C NMR (100 MHz, acetone-d_6): δ=28.13 (C-11, C-12, C-13), 43.07 (C-7), 74.51 (C-1), 74.78 (C-2), 83.50 (C-10), 98.46 (C-6), 129.84 (C-4), 144.42 (C-5), 153.94 (C-8), 159.98 (C-9), 198.17 (C-3); MS (150°C): *m*/*z* (%)=227 (M-^{t}Bu+1, 211 (9), 210 (100), 181 (3), 136 (17), 123 (3), 87 (4), 83 (41); HRMS: *m*/*z* for $C_9H_9NO_6$ calcd: 227.0430, found: 227.0430.

Diol carboxylic acid 25. To a solution of **24** (10 mg, 0.035 mmol) in dichloromethane (1 ml) was added trifluoroacetic acid (1 ml). After 1 h at room temperature the reaction mixture was concentrated and 8 mg of acid **25** were obtained as a brown oil; $[\alpha]_D^{20}$=44.4° (*c*=1.08, MeOH); IR ($CHCl_3$): ν=3411 cm^{-1} (s), 2925 (m.), 1703 (s), 1599 (m), 1514 (w), 1257 (m), 1162 (m), 1116 (m), 918 (m), 736 (w); ^1H NMR (400 MHz, acetone-d_6): δ=3.31 (d, *J*=18 Hz, 1H, 7-H), 3.78 (d, *J*=18 Hz, 1H, 7-H), 4.19 (dd, *J*=2/2.5 Hz, 1H, 1-H), 4.55 (d, *J*=2.5 Hz, 1H, 2-H), 6.15 (d, *J*=10 Hz, 1H, 4-H), 6.85 (d, *J*=2/10 Hz, 1H, 5-H); ^{13}C NMR (100 MHz, acetone-d_6): δ=42.93 (C-7), 74.54 (C-1), 74.80 (C-2), 89.80 (C-6), 129.95 (C-4), 144.36 (C-5), 153.20 (C-8), 161.54 (C-9), 198.18 (C-3); MS (70°C):

m/z (%)=228 (M+1, 3), 227 (M^+, 11), 223 (17), 211 (10), 210 (100), 198 (10), 182 (13), 164 (7), 140 (12), 123 (12), 109 (7), 96 (20), 84 (9); HRMS: *m/z* for $C_9H_9NO_6$ calcd: 227.0430, found: 227.0434.

Epoxy adduct 26. To a solution of adduct **21** (35 mg, 0.072 mmol) in dry dichloromethane (3 ml) were added *tert*-BuOOH (0.05 ml, 44 mg, 0.384 mmol, 5.5 equiv., 80% in *tert*-butylperoxide) and two drops of DBU. After stirring overnight the reaction mixture was quenched with sat. aq. $Na_2S_2O_5$, extracted with methyl-*tert*-butyl ether and concentrated. Purification of the raw material yielded 20 mg (80%) of epoxide **26** as a yellow foam; $[\alpha]_D^{20}=37.2°$ (*c*=0.65, $CHCl_3$); IR ($CHCl_3$): ν=2984 cm^{-1} (m), 2933 (m), 1716 (s), 1594 (m), 1516 (s), 1461 (w), 1443 (w), 1385 (m), 1352 (m), 1275 (m), 1252 (s), 1181 (m), 1149 (m), 1130 (m), 909 (m), 822 (m); ^{1}H NMR (400 MHz, $CDCl_3$): δ=0.56 (d_{br}, *J*=13 Hz, 1H, 2-H_{eq}), 0.76 (s, 3H, 28-H), 1.12–1.66 (m, 5H), 1.58 (s, 9H, 20-H, 21-H, 22-H), 1.73 (d_{br}, *J*=12 Hz, 1H), 1.99 (dtr, *J*=3.5/13 Hz, 1H), 3.04 (d, *J*=10 Hz, 1H, 11-H), 3.35 (d, *J*=4 Hz, 1H, 13-H), 3.37 (d, *J*=4 Hz, 1H, 14-H), 3.39 (d, *J*=18.5 Hz, 1H, 16-H), 3.64 (d, *J*=18.5 Hz, 1H, 16-H), 3.79 (s, 3H, 27-H), 3.96 (d, *J*=10 Hz, 1H, 10-H), 6.06 (d, *J*=5.5 Hz, 1H, 7-H), 6.14 (d, *J*=5.5 Hz, 1H, 8-H), 6.85 (d, *J*=9 Hz, 2H, 25-H, 25′-H), 7.12 (d, *J*=9 Hz, 2H, 24-H, 24′-H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=15.77 (C-27), 21.06 (C-4), 23.34 (C-3), 26.89 (C-5), 26.92 (C-2), 28.06 (C-20, C-21, C-22), 46.35 (C-16), 52.64 (C-11), 53.07 (C-10), 55.18 (C.27), 56.00 (C-13), 60.31 (C-6), 60.58 (C-14), 61.01 (C-1), 63.86 (C-9), 84.09 (C-19), 88.55 (C-12), 113.46 (C-25, C-25′), 127.71 (C.24, C-24′), 130.43 (C-23), 135.64 (C-7), 139.00 (C-8), 152.30 (C-26), 158.09 (C-17), 159.39 (C-18), 204.29 (C-15); MS (180°C): *m/z* (%)=266 (dienophile+1, 2), 240 (diene, 100), 197 (6), 121 (3); FAB-MS: *m/z* (%)=528 (M+23, 7), 506 (M+1, 4), 505 (M^+, 4), 504 (M−1, 4), 241 (74), 240 (100).

Spiroisoxazoline epoxide 27. *Method A:* Epoxyadduct **26** (15 mg, 0.030 mmol) was brought into a flash vacuum pyrolysis apparatus and sublimed at 300°C/1.510^{-2} mbar through a pyrolysis tube heated to 300°C. After 2 h the whole starting material was sublimed off and a 1:1 mixture of **27** and diene **5** was trapped on a cooling finger. Chromatographic purification yielded 1 mg (13%) of **27** as a colorless oil.

Method B: To a solution of bromohydrine **28** (20 mg, 0.057 mmol) in dichloromethane (3 ml) was added a catalytic amount of DBU. The reaction mixture was concentrated and chromatographic purification yielded 16 mg (95%) of **27** as a colorless oil; $[\alpha]_D^{20}=195.1°$ (*c*=0.50, $CHCl_3$); IR ($CHCl_3$): ν=2984 cm^{-1} (m), 1710 (s), 1597 (m), 1269 (s), 1140 (m); ^{1}H NMR (400 MHz, $CDCl_3$): δ=1.58 (s, 9H, 11-H, 12-H, 13-H), 3.33 (d, *J*=18 Hz, 1H, 7-H), 3.58 (dd, *J*=2/3.5 Hz, 1H, 1-H), 3.68 (d, *J*=18 Hz, 1H, 7-H), 3.76 (dd, *J*=2.5/3.5 Hz, 1H, 2-H), 6.09 (dd, *J*=10.5/2 Hz, 1H, 4-H), 6.45 (dd, *J*=2.5/10 Hz, 1H, 5-H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=28.01 (C-11, C-12, C-13), 44.20 (C-7), 53.55 (C-1), 57.29 (C-2), 83.40 (C-10), 84.48 (C-6), 128.30 (C-4), 141.24 (C-5), 152.79 (C-8), 158.66 (C-9), 191.27 (C-3); MS (150°C): *m/z* (%)=266 (M+1, 3), 251 (14), 209 (59), 192 (100), 164 (16), 123 (10); HRMS: *m/z* for $C_{13}H_{15}NO_5$ calcd: 265.0950, found: 265.0949.

Bromohydrinmethylester 14b. To a solution of PPh_3 (240 mg, 0.916 mmol, 2.2 equiv.) in dry dichloromethane (10 ml) was added a bromine solution (0.95 ml, 0.5 M in dichloromethane, 0.475 mmol, 1.1 equiv.) at 0°C. Afterwards Hünig's base (0.09 ml, 0.548 mmol, 1.3 equiv.) and TsCl (26 mg, 0.137 mmol, 0.3 equiv.) were added and the reaction mixture was stirred for 10 min. Then diol **13** (100 mg, 0.415 mmol) was added and the mixture was stirred overnight at room temperature. The reaction was stopped with water, extracted with ethyl acetate, dried ($MgSO_4$) and chromatographic purification yielded 71 mg (72%) of **14b** as a yellow oil; IR ($CHCl_3$): ν=3592 cm^{-1} (w), 3040 (w), 2956 (w), 2928 (w), 1728 (s), 1704 (s), 1600 (m), 1444 (m), 1373 (m), 1352 (s), 1264 (m), 1124 (m), 920 (m); ^{13}C NMR (100 MHz, $CDCl_3$): δ=37.46 (C-7), 53.14/53.16 (C-10), 57.32 (C-1), 75.03 (C-2), 90.14 (C-6), 127.80 (C-4), 147.39 (C-5), 151.01/152.10 (C-8), 160.13/160.18 (C-9), 188.20 (C-3); MS (140°C): *m/z* (%)=274 (M-31, 5), 272 (M-31, 5), 224 (89), 192 (32), 181 (30), 154 (13), 138 (28), 122 (22), 96 (100), 77 (19), 68 (36); HRMS: *m/z* for $C_9H_7NO_4Br$ calcd: 271.9558, found: 271.9557; main product (*trans*-bromohydrin): ^{1}H NMR (400 MHz, $CDCl_3$): δ=3.10 (d, *J*=18 Hz, 1H, 7-H), 3.92 (d, *J*=18 Hz, 1H, 7-H), 3.96 (s, 3H, 10-H), 4.41 (dd, *J*=3/12 Hz, 1H, 1-H), 4.57 (d, *J*=12 Hz, 1H, 2-H), 6.27 (d, *J*=10 Hz, 1H, 4-H), 7.01 (d, *J*=10 Hz, 1H, 5-H); the spectroscopic data were taken from the spectra of the mixtures; side product (*cis*-bromohydrin): ^{1}H NMR (400 MHz, $CDCl_3$): δ=3.24 (d, *J*=18 Hz, 1H, 7-H), 3.97 (s, 3H, 10-H), 4.44 (d, *J*=18 Hz, 1H, 7-H), 4.48 (s_{br}, 1H, 1-H), 4.98 (s_{br}, 1H, 2-H), 6.25 (d, *J*=10 Hz, 1H, 4-H), 6.76 (d, *J*=10 Hz, 1H, 5-H); the spectroscopic data were taken from the spectra of the mixtures.

Bromohydrin-*tert*-butylester 28. To a solution of PPh_3 (119 mg, 0.456 mmol, 4.3 equiv.) in dry dichloromethane (3 ml) was added a bromine solution (0.28 ml, 0.5 M in dichloromethane, 0.139 mmol, 1.3 equiv.) at 0°C. Afterwards Hünig's base (3 drops) and TsCl (20 mg, 0.106 mmol, 1 equiv.) were added and the reaction mixture was stirred for 10 min. Then diol **24** (30 mg, 0.106 mmol) was added and the mixture was stirred for 14 h at room temperature. No working up followed, chromatographic purification yielded 16 mg (44%) of **28** as a yellow oil; IR ($CHCl_3$): ν=3590 cm^{-1} (w), 2984 (m), 1712 (s), 1601 (w), 1264 (m), 1129 (s); FAB-MS: *m/z* (%)=369 (M+23, 7), 348 (M^+, 9), 329 (18), 307 (36), 289 (23), 259 (32), 176 (27), 154 (100), 137 (82); main product (*cis*-bromohydrin): ^{1}H NMR (400 MHz, $CHCl_3$): δ=1,57 (s, 9H, 11-H, 12-H, 13-H), 3.01 (d, *J*=18 Hz, 1H, 7-H), 3.83 (d, *J*=18 Hz, 1H, 7-H), 4.38 (m, 1H, 2-H), 4.97 (s_{br}, 1H, 1-H), 6.20 (d, *J*=10 Hz, 1H, 4-H), 6.97 (d, *J*=10 Hz, 1H, 5-H); ^{13}C-NMR (100 MHz, $CDCl_3$): δ=28.01 (C-11, C-12, C-13), 37.73 (C-7), 57.27 (C-1), 75.03 (C-2), 84.27 (C-10), 89.83 (C-6), 127.55 (C-4), 147.84 (C-5), 152.38 (C-8), 158.83 (C-9), 188.25 (C-3); the spectroscopic data were taken from the spectra of the mixtures; side product (*trans*-bromohydrin): ^{1}H NMR (400 MHz, $CDCl_3$): δ=1.56 (s, 9H, 11-H, 12-H, 13-H), 3.16 (d, *J*=18 Hz, 1H, 7-H), 3.93 (d, *J*=18 Hz, 1H, 7-H), 4.38 (m, 1H. 1-H), 4.50 (d, *J*=12 Hz, 1H, 2-H), 6.20 (d, *J*=10 Hz, 1H, 4-H), 6.70 (d, *J*=10 Hz, 1H, 5-H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=28.01 (C-11, C-12, C-13), 37.73 (C-7), 57.27 (C-1),

75.03 (C-2), 84.33 (C-10), 88.36 (C-6), 127.55 (C-4), 147.84 (C-5), 153.44 (C-8), 158.71 (C-9), 188.84 (C-3); the spectroscopic data were taken from the spectra of the mixtures.

Epoxymethylester 30a. To a solution of bromohydrin **14** (50 mg, 0.165 mmol) in dichloromethane (5 ml) was added a catalytic amount of DBU. The reaction mixture was concentrated and chromatographic purification yielded 33 mg (90%) of **30a** as a white solid; $[\alpha]_D^{20}=275.5°$ ($c=0.79CHCl_3$); melting point=77.4°C; IR ($CHCl_3$): $\nu=3040\ cm^{-1}$ (w), 2956 (w), 2928 (w), 1728 (s), 1692 (s), 1596 (m), 1444 (m), 1372 (m), 1260 (s), 1228 (m), 1124 (m), 912 (m); ^1H NMR (400 MHz, $CDCl_3$): $\delta=3.37$ (d, $J=18$ Hz, 1H, 7-H), 3.59 (dd, $J=2/4$ Hz, 1H, 1-H), 3.70–3.77 (m, 2H, 2-H, 7-H), 3.95 (s, 3H, 10-H), 6.12 (dd, $J=2/10$ Hz, 1H, 4-H), 6.46 (dd, $J=3/10$ Hz, 1H, 5-H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta=43.88$ (C-7), 53.23 (C-10), 53.51 (C-1), 57.14 (C-2), 83.81 (C-6), 128.53 (C-4), 140.87 (C-5), 151.46 (C-8), 160.02 (C-9), 191.14 (C-3); MS (90°C): *m/z* (%)=223 (M^+, 49), 206 (10), 194 (29), 174 (11), 164 (17), 146 (37), 136 (24), 119 (20), 94 (100), 77 (26), 66 (53); HRMS: *m/z* for $C_{10}H_9NO_5$ calcd: 223.0481, found: 223.0484.

Epoxy carboxylic acid 30b. To a solution of **27** (16 mg, 0.060 mmol) in dichloromethane (0.75 ml) was added trifluoroacetic acid (0.75 ml). After 2 h at room temperature the reaction mixture was concentrated and 13 mg (quant.) of acid **30b** were obtained as a brown oil; $[\alpha]_D^{20}=199.7°$ ($c=0.34$, MeOH); IR ($CHCl_3$): $\delta=3494\ cm^{-1}$ (w), 2927 (m), 1694 (s), 1599 (m), 1263 (m); ^1H NMR (400 MHz, acetone-d_6): $\delta=3.56$ (d, $J=18$ Hz, 1H, 7-H), 3.61 (dd, $J=3.5/2$ Hz, 1H, 2-H), 3.73 (d, $J=18$ Hz, 1H, 7-H), 4.02 (dd, $J=2.5/3.5$ Hz, 1H, 1-H), 6.10 (dd, $J=2/10$ Hz, 1H, 4-H), 6.80 (dd, $J=2.5/10$ Hz, 1H, 5-H); ^{13}C NMR (100 MHz, acetone-d_6): $\delta=45.45$ (C-7), 55.27 (C-1), 59.09 (C-2), 85.61 (C-6), 129.42 (C-4), 144.35 (C-5), 154.50 (C-8), 162.22 (C-9), 193.85 (C-3); MS (140°C): *m/z* (%): 210 (M+1, 2), 209 (M^+, 13), 180 (7), 165 (10), 149 (16), 125 (38), 97 (100); HRMS: *m/z* for $C_9H_7NO_5$ calcd: 209.0324, found: 209.0324.

Bromoepoxymethylester 29a. To a solution of **30a** (20 mg, 0.090) in dry dichloromethane (3 ml) was added a solution of bromine in dry dichloromethane (0.21 ml, 0.5 M, 0.108 mmol, 1.2 equiv.) at 0°C. After 1 h Hünig's base (0.03 ml, 0.179 mmol, 2 equiv.) was added at 0°C. The solution was stirred for 5 h at room temperature and then extracted with methyl-*tert*-butyl ether. The organic layer was washed with water, dried ($MgSO_4$) and concentrated. Purification by flash chromatography yielded 22 mg (83%) of **29a** as a yellow solid; $[\alpha]_D^{20}=202.8°$ ($c=0.64$, $CHCl_3$); melting point=158.0°C; IR ($CHCl_3$): $\delta=3040\ cm^{-1}$ (w), 2956 (w), 1728 (s), 1708 (s), 1596 (m), 1444 (m), 1376 (w), 1260 (s), 1140 (m), 908 (m); ^1H NMR (200 MHz, $CDCl_3$): $\delta=3.41$ (d, $J=18$ Hz, 1H, 7-H), 3.68–3.82 (m, 3H, 1-H, 2-H, 7-H), 3.95 (s, 3H, 10-H), 6.92 (d_{br}, $J=2$ Hz, 1H, 5-H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta=44.78$ (C-7), 54.35 (C-10), 54.37 (C-1), 58.10 (C-2), 86.37 (C-6), 126.30 (C-4), 142.01 (C-5), 152.41 (C-8), 160.78 (C-9), 185.59 (C-3); MS (110°C): *m/z* (%)=304 (M+1, 5), 303 (M^+, 35), 302 (M+1, 6), 301 (M^+, 41), 286 (14), 284 (12), 272 (32), 242 (43), 222 (48), 203 (45), 194 (75), 172 (61), 162 (32), 146 (50), 93 (100), 77 (36), 66 (83); HRMS: *m/z* for $C_{10}H_8NO_5$ calcd: 222.0402, found: 222.0406.

Bromoepoxide-*tert*-butylester 29b. To a solution of **27** (15 mg, 0.057 mmol) in dry dichloromethane (2 ml) was added a solution of bromine in dry dichloromethane (0.11 ml, 0.5 M, 0.057 mmol, 1 equiv.) at 0°C. After 3 h stirring at room temperature Hünig's base (4 drops) was added. The solution was stirred for 30 min at room temperature and then the reaction was stopped by flash chromatography. The yield was 18 mg (93%) of **29b** as a yellow oil; $[\alpha]_D^{20}=172.1°$ ($c=0.82$, $CHCl_3$); IR ($CHCl_3$): $\nu=2984\ cm^{-1}$ (w), 1710 (s), 1599 (m), 1260 (m), 1142 (m); ^1H NMR (400 MHz, $CDCl_3$): $\delta=1.58$ (s, 9H, 11-H, 12-H, 13-H), 3.38 (d, $J=18$ Hz, 1H, 7-H), 3.69 (d, $J=18$ Hz, 1H, 7-H), 3.72 (d, $J=3.5$ Hz, 1H, 2-H), 3.80 (dd, $J=3.5/2.5$ Hz, 1H, 1-H), 6.39 (d, $J=2.5$ Hz, 1H, 5-H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta=31.15$ (C-11, C-12, C-13), 46.27 (C-7), 55.78 (C-1), 86.86 (C-10), 87.14 (C-6), 127.15 (C-4), 143.57 (C-5), 154.90 (C-8), 160.56 (C-9), 186.85 (C-3); MS (120°C): *m/z* (%)=364 (M+19, 10), 362 (M+19, 9), 345 (M^+, 5), 343 (M^+, 4), 330 (10), 328 (11), 289 (3), 287 (24), 272 (57), 270 (60), 244 (27), 242 (27), 149 (21), 84 (100); HRMS: *m/z* for $C_9H_{14}BrNO_5$ calcd: 269.9402, found: 269.9402.

Bromoepoxy carboxylic acid 29c. To a solution of **29b** (18 mg, 0.052 mmol) in dichloromethane (1 ml) was added trifluoroacetic acid (1 ml). After 2 h at room temperature the reaction mixture was concentrated and 15 mg (quant.) of acid **29c** were obtained as a brown oil; $[\alpha]_D^{20}=171.4°$ ($c=0.69$, MeOH); ^1H NMR (400 MHz, acetone-d_6): $\delta=3.68$ (d, $J=18$ Hz, 1H, 7-H), 3.79 (d, $J=18$ Hz, 1H, 7-H), 3.89 (d, $J=3.5$ Hz, 1H, 2-H), 4.14 (dd, $J=2.5/3.5$ Hz, 1H, 1-H), 7.41 (d, $J=2.5$ Hz, 1H, 5-H); ^{13}C NMR (100 MHz, acetone-d_6): $\delta=44.22$ (C-7), 54.18 (C-1), 58.04 (C-2), 86.17 (C-6), 124.37 (C-4), 143.82 (C-5), 153.51 (C-8), 160.93 (C-9), 186.23 (C-3); MS (150°C): *m/z* (%): 289 (M^+, 4), 287 (4), 205 (92), 177 (15), 175 (18), 123 (25), 121 (26); HRMS: *m/z* for $C_9H_6BrNO_5$ calcd: 286.9429, found: 286.9416.

Bromoepoxyamide 31. To a solution of acid **29c** (25 mg, 0.087 mmol) in dry THF (2 ml) was added Staab's reagent (14 mg, 0.087 mmol, 1 equiv.) at room temperature. The solution was stirred for 10 min, then benzylamine (9 mg, 0.087 mmol, 1 equiv.) was added at room temperature. After stirring the reaction mixture for 10 min, it was worked up by purification by flash chromatography. In this way 19 mg (58%) of **31** were obtained as a yellow solid; $[\alpha]_D^{20}=146.1°$ ($c=0.64$, $CHCl_3$); melting point=158.0°C; IR ($CHCl_3$): $\delta=3417\ cm^{-1}$ (m), 3043 (w), 2929 (w), 1707 (s), 1681 (s), 1602 (m), 1530 (s), 1340 (w), 1252 (m), 910 (m); UV ($CHCl_3$): $\lambda_{max}=280$ nm; ^1H NMR (400 MHz, $CDCl_3$): $\delta=3.45$ (d, $J=18$ Hz, 7-H), 3.78 (m, 3H, 7-H, 2-H, 1-H), 4.55 (d, $J=6$ Hz, 2H, 10-H), 6.91 (d, $J=2.5$ Hz, 1H, 5-H), 6.94 (tr_{br}, $J=7$ Hz, 1H, NH), 7.35 (m, 5H, 11-H, 12-H, 13-H, 11′-H, 12′-H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta=43.46$ (C-7), 43.79 (C-10), 53.37 (C-1), 57.16 (C-2), 85.05 (C-6), 125.04 (C-4), 127.97 (C-13, C-13′), 128.04 (C-14), 128.95 (C-12, C-12′), 136.94 (C-11), 141.35 (C-5), 153.98 (C-8), 158.14 (C-9), 184.80 (C-3); MS (160°C): *m/z* (%): 378 (M^+, 3), 376 (M^+, 3), 344 (3), 341

(3), 256 (1), 254 (2), 228 (2), 174 (17), 173 (15), 132 (14), 107 (88), 91 (100); HRMS: *m/z* for $C_{16}H_{13}N_2O_4$ calcd: 376.0059, found: 376.0060.

Bromohydrinamide 32. To a solution of PPh_3 (16 mg, 0.061 mmol, 1.2 equiv.) in dry dichloromethane (2 ml) was added a solution of bromine in dry dichloromethane (0.10 ml, 0.5 M, 0.051 mmol, 1.0 equiv.) at 0°C. After 5 min at 0°C **31** (19 mg, 0.051 mmol) was added. After 2 h at room temperature the reaction was stopped by flash chromatography. In this way 16 mg (70%) of **32** were obtained as a yellow oil (diasteromeric mixture, *trans*:*cis*-bromohydrin=93:7); IR ($CHCl_3$): ν=3593 cm^{-1} (w), 3417 (m), 2928 (w), 1715 (s), 1678 (s), 1605 (m), 1531 (s), 1315 (w), 1258 (m), 910 (s), 792 (s); ^{13}C NMR (100 MHz, $CDCl_3$): δ=37.37 (C-7), 43.71 (C-10), 55.87 (C-1), 74.39 (C-2), 90.51 (C-6), 122.68 (C-4), 127.94 (C-13, C-13′), 128.90 (C-12, C-12′), 136.99 (C-11), 147.62 (C-5), 153.64 (C-8), 158.48 (C-9), 181.82 (C-3); MS (190°C): *m/z* (%): 460 (M^+, 1), 458 (M^+, 2), 456 (M^+,1), 361 (7), 359 (6), 341 (1), 291 (2), 241 (3), 175 (17), 106 (100), 91 (97); HRMS: *m/z* for $C_{16}H_{14}Br_2O_4N_2$ calcd: 455.9320, found: 455.9322; main product (*trans*-bromohydrin): ^1H NMR (400 MHz, $CDCl_3$): δ=3.16 (d, *J*=18 Hz, 1H, 7-H), 3.38 (d, *J*=3 Hz, 1H, OH), 3.91 (d, *J*=18 Hz, 1H 7-H), 4.32 (dd_{br}, *J*=2/12 Hz, 1H, 1-H), 4.50 (dd, *J*=6/15 Hz, 1H, 10-H), 4.56 (dd, *J*=6/15 Hz, 1H, 10-H), 4.58 (d, *J*=12 Hz, 1H, 2-H), 6.39 (tr_{br}, *J*=6 Hz, 1H, NH), 7.33 (m, 6H, 5-H, 12-H, 13-H, 14-H, 12′-H, 13′-H); the spectroscopic data were taken from the spectra of the mixtures; side product (*cis*-bromohydrine): ^1H NMR (400 MHz, $CDCl_3$): δ=3.28 (d, *J*=18 Hz, 1H, 7-H), 3.98 (d, *J*=18 Hz, 1H, 7-H), 4.37 (s_{br}, 1H, 1-H), 4.53 (m, 3H, 10-H, 2-H), 7.11 (d, *J*=1 Hz, 1H, 5-H), 7.33 (m, 5H, 12-H, 13-H, 14-H, 12′-H, 13′-H); the spectroscopic data were taken from the spectra of the mixtures.

Mentholbromide 34. To a solution of PPh_3 (738 mg, 2.821 mmol, 2.2 equiv.) in dry dichloromethane (10 ml) was added a bromine solution (3.33 ml, 0.5 M in dichloromethane, 1.67 mmol, 1.3 equiv.) at 0°C. Afterwards NEt_3 (0.23 ml, 1.67 mmol, 1.3 equiv.) and TsCl (49 mg, 0.256 mmol, 0.2 equiv.) were added and the reaction mixture was stirred for 10 min. Then menthol (200 mg, 1.282 mmol) was added and the mixture was stirred for 1.5 h at room temperature. The reaction was stopped with water, extracted with ethyl acetate, dried ($MgSO_4$) and chromatographic purification yielded 479 mg (86%) of **34** as a colorless oil; IR ($CHCl_3$): ν=2948 cm^{-1} (s), 2924 (s), 2868 (m), 2844 (m), 1480 (w), 1456 (m), 1384 (w), 1368 (w), 1272 (m), 1228 (m), 1188 (m); ^1H NMR (400 MHz, $CDCl_3$): δ=0.78 (m, 1H), 0.89 (d, *J*=7 Hz, 3H, 10-H), 0.92 (s_{br}, 3H, 8-H), 0.93 (s_{br}, 3H, 9-H), 1.31–1,59 (m, 3H), 1.70–1.79 (m, symmetric, 2H), 1.90–2.02 (m, 1H), 2.16 (dq, *J*=4/14 Hz, 1H), 4.65–4.69 (m, 1H, 1-H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=20.09/20.66/27.78 (CH_3), 25.08 (CH_2), 26.79 (CH), 31.39 (CH), 34.85 (CH_2), 43.94 (CH_2), 49.27 (CH), 60.65 (C-1); MS (RT): *m/z* (%)=139 (M-Br, 81), 123 (13), 109 (3), 95 (51), 83 (100), 81 (41), 69 (36); HRMS: *m/z* for $C_{10}H_{19}$ calcd: 139.1487, found: 139.1487.

β-Androsteronebromide 35a. To a solution of PPh_3 (415 mg, 1.59 mmol, 2.3 equiv.) in dry dichloromethane (10 ml) was added a bromine solution (1.79 ml, 0.5 M in dichloromethane, 0.897 mmol, 1.3 equiv.) at 0°C. Afterwards Hünig's base (0.15 ml, 0.897 mmol, 1.3 equiv.) and TsCl (26 mg, 0.137 mmol, 0.2 equiv.) were added and the reaction mixture was stirred for 10 min. Then *cis*-androsterone (200 mg, 0.690 mmol) was added and the mixture was stirred over night at room temperature. The reaction was stopped with water, extracted with ethyl acetate, dried ($MgSO_4$) and chromatographic purification yielded 208 mg (70%) of **35a** as a white solid; melting point=136.7°C; IR ($CHCl_3$): ν=2936 cm^{-1} (m), 2852 (m), 1732 (s), 1464 (w), 1452 (w), 1372 (w), 1160 (w), 908 (m); ^1H NMR (400 MHz, $CDCl_3$): δ=0.71 (dtr, *J*=4/12 Hz, 1H), 0.86 (s, 3H, 18-H), 0.88 (s, 3H, 19-H), 0.94 (dd, *J*=5/12 Hz, 1H), 1.10 (dd, *J*=5/12 Hz, 1H), 1.05 (dtr, *J*=4/14 Hz, 1H), 1.14–2.19 (m, 13H), 2.44 (ddd, *J*=1/10/18 Hz, 1H, 16-H), 3.98–4.05 (m, symmetric, 1H, 3-H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=12.28 (C-18), 13.80 (C-19), 20.31 (CH_2), 21.73 (CH_2), 28.09 (CH_2), 30.72 (CH_2), 31.48 (CH_2), 31.48 (CH_2), 34.06 (CH_2), 34.92 (CH), 35.51 (C), 35.80 (CH_2), 35.70 (CH_2), 40.47 (CH_2), 47.75 (C), 47.95 (CH), 51.12 (CH), 52.12 (CH), 54.32 (CH), 221 (C); MS (RT): *m/z* (%)=354 (M^+, 13), 352 (14), 310 (4), 295 (3), 273 (3), 217 (3), 107 (6), 69 (38); HRMS: *m/z* for $C_{19}H_{29}BrO$ calcd: 352.1402, found: 352.1404; elemental analysis: calcd: C: 64.59, H: 8.27; found: C: 64.96, H: 8.51.

α-Androsteronebromide 35b. To a solution of PPh_3 (415 mg, 1.59 mmol, 2.3 equiv.) in dry dichloromethane (10 ml) was added a bromine solution (1.79 ml, 0.5 M in dichloromethane, 0.897 mmol, 1.3 equiv.) at 0°C. Afterwards Hünig's base (0.15 ml, 0.897 mmol, 1.3 equiv.) and TsCl (26 mg, 0.137 mmol, 0.2 equiv.) were added and the reaction mixture was stirred for 10 min. Then *trans*-androsterone (200 mg, 0.690 mmol) was added and the mixture was stirred over night at room temperature. The reaction was stopped with water, extracted with ethyl acetate, dried ($MgSO_4$) and chromatographic purification yielded 225 mg (93%) of **35b** as a white solid; melting point=168.0°C; IR ($CHCl_3$): ν=2932 cm^{-1} (m), 2860 (m), 1732 (s), 1452 (m), 1368 (w), 1252 (m), 1052 (m), 1012 (m), 908 (m); ^1H NMR (400 MHz, $CDCl_3$): δ=0.81 (s, 3H, 18-H), 0.86 (s, 3H, 19-H), 0.88–1.99 (m, 16H), 2.08 (dtr, *J*=9/18 Hz, 1H, 16-H), 2.41 (dd, *J*=8/18 Hz, 1H, 16-H), 4.73 (q, *J*=3 Hz, 1H, 3-H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=12.33 (C-18), 13.83 (C-19), 20.05 (CH_2), 21.73 (CH_2), 27.57 (CH_2), 30.63 (CH_2), 30.94 (CH_2), 31.51 (CH_2), 32.85 (CH_2), 34.99 (CH), 35.82 (CH_2), 36.39 (C), 37.22 (CH_2), 40.16 (CH), 47.77 (C), 51.42 (CH), 53.98 (CH), 55.59 (CH), 221.17 (C); MS (130°C): *m/z* (%)=355 (M+1, 23), 354 M^+, 95), 353 (M+1, 24), 352 (M^+, 100), 319 (12), 310 (30), 296 (24), 282 (20), 218 (35), 164 (10), 147 (13), 123 (20), 121 (19), 97 (26), 95 (20), 93 (30), 81 (24); HRMS: *m/z* for $C_{19}H_{29}BrO$ calcd: 352.1402, found: 352.1401; elemental analysis: calcd: C: 64.59, H: 8.27; found: C: 64.83, H 8.27.

Protected bromodiolmethylester. To a solution of **17** (200 mg, 0.557 mmol) in dry dichloromethane (4 ml) was added a solution of bromine in dry dichloromethane (1.1 ml, 0.5 M, 0.557 mmol, 1 equiv.) at 0°C. After 1 h stirring at 0°C Et_3N (24 mg, 0.244 mmol, 4 equiv.) was added. The solution was stirred for 3 h at room temperature and then the reaction was stopped with water, extracted with methyl-*tert*-butyl ether and dried ($MgSO_4$). Purification by flash

chromatography yielded 217 mg (89%) of the protected bromodiolmethylester as a yellow foam; IR ($CHCl_3$): ν=3040 cm^{-1} (w), 2956 (w), 2932 (w), 2856 (w), 1728 (s), 1612 (m), 1516 (m), 1444 (m), 1376 (w), 1252 (s), 1096 (m), 908 (m); ^1H NMR (400 MHz, $CDCl_3$): δ=3.30/3.32 (d, J=18 Hz, 1H, 7-H), 3.77–3.95 (m, 7-H, 16-H, 10-H), 4.52/4.61 (dd, J=2/5 Hz, 1H, 1-H), 4.82/4.97 (d, J=5 Hz, 1H, 2-H), 5.95/5.96 (s, 1H, 11-H), 6.86–6.93 (m, 2H, 14-H, 14′-H), 7.19 (d, J=2 Hz, 1H, 5-H), 7.24/7.35 (d, J=9 Hz, 1H, 13-H, 13′-H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=40.84/40.93 (C-7), 51.26 (C-16), 53.31/53.32 (C-10), 72.24/73.64 (C-1), 74.56/76.33 (C-2), 83.81/84.01 (C-6), 102.02/103.37 (C-11), 111.88/111.93 (C-14, C-14′), 125.04/126.71 (C-12), 125.63/126.17 (C-13, C-13′), 141.37/142.13 (C-5), 149.60/149.71 (C-15), 157.87 (C-8), 158.70/158.92 (C-9); FAB-MS: m/z (%)=462 (M+23, 6), 460 (M+23, 6), 429 (7), 401 (16), 355 (20), 341 (23), 325 (27), 281 (84), 267 (31), 249 (17), 221 (81), 207 (100), 191 (33), 176 (13).

Bromodiolmethylester 36. To a solution of protected bromodiolmethylester (19 mg, 0.043 mmol) in aq. acetone (3 ml) was added a catalytic amount of 2 N aq. H_2SO_4 at room temperature. After 4 h the reaction was stopped with $NaHCO_3$. The reaction mixture was concentrated and afterwards water was added. The aqueous phase was extracted with ethyl acetate. The combined organic layers were dried ($MgSO_4$) and concentrated. Chromatographic prurification yielded 9 mg (65%) of **36** as a yellow foam; $[\alpha]_D^{20}$=132.5° (c=0.28, $CHCl_3$); IR ($CHCl_3$): ν=3576 cm^{-1} (w), 3524 (w), 2956 (w), 2928 (w), 2856 (w), 1732 (s), 1596 (w), 1444 (m), 1376 (m), 1296 (m), 1252 (s), 1128 (m), 1112 (m); ^1H NMR (400 MHz, $CDCl_3$): δ=2.83 (d, J=2 Hz, 1H, OH), 3.29 (d, J=18 Hz, 1H, 6-H), 3.66 (d, J=2 Hz, 1H, OH), 3.90 (d, J=18 Hz, 1H, 7-H), 3.99 (s, 3H, 10-H), 4.28–4.32 (m, 1H, 1-H), 4.81–4.85 (m, 1H, 2-H), 7.08 (d, J=2 Hz, 1H, 5-H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=42.66 (C-7), 53.22 (C-10), 73.03 (C-1), 73.57 (C-2), 88.49 (C-6), 124.77 (C-4), 143.22 (C-5), 160.56 (C-9), 191.05 (C-3); MS (130°C): m/z (%)=7.13 (M^+, 6), 319 (M^+, 7), 290 (13), 259 (14), 244 (12), 216 (20), 202 (19), 176 (91), 174 (100), 152 (12), 124 (12), 99 (23), 78 (19), 69 (37).

Bromohydrinmethylester 38. To a solution of PPh_3 (25 mg, 0.095 mmol, 1.5 equiv.) in dry dichloromethane (2 ml) was added a solution of bromine in dry dichloromethane (0.13 ml, 0.5 M, 0.063 mmol, 1.0 equiv.) at 0°C. After 5 min at 0°C **36** (19 mg, 0.063 mmol) was added. After 2 h at room temperature the reaction was stopped with water, extracted with ethyl acetate and dried ($MgSO_4$). Purification by flash chromatography yielded 23 mg (96%) of **38** as a yellow oil (diastereomeric mixture, *trans*:*cis*-bromohydrin=1:2); IR ($CHCl_3$): ν=3584 cm^{-1} (w), 3040 (w), 2956 (w), 2928 (w), 1728 (s), 1600 (m), 1444 (m), 1376 (m), 1260 (s), 1128 (m), 908 (s); MS (rt): m/z (%)=305 (M-78, 5), 303 (M-78, 4), 281 (4), 271 (10), 261 (3), 242 (3), 222 (8), 212 (4), 176 (3), 149 (4), 99 (10), 85 (68), 83 (100), 77 (7); HRMS: m/z for $C_{10}H_{10}NO_5Br$ calcd: 302.9743, found: 302.9745; main product (*cis*-bromohydrine): ^1H NMR (400 MHz, $CDCl_3$): δ=3.12 (d, J=18 Hz, 1H, 7-H), 3.87 (d, J=18 Hz, 1H, 7-H), 3.92 (s, 3H, 10-H), 4.37 (dd, J=3/12 Hz, 1H, 1-H), 4.56 (d, J=12 Hz, 1H, 2-H), 7.41 (s, 1H, 5-H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=37.28 (C-7), 53.27 (C-10), 55.56 (C-2), 74.45 (C-1), 90.80 (C-6), 123.01 (C-4), 147.29 (C-5), 152.11 (C-8), 159.97 (C-9), 181.72 (C-3); the spectroscopic data were taken from the spectra of the mixtures; side product (*trans*-bromohydrin): ^1H NMR (400 MHz, $CDCl_3$): δ=3.26 (d, J=18 Hz, 1H, 7-H), 3.93 (s, 3H, 10-H), 3.97 (d, J=18 Hz, 1H, 7-H), 4.44 (s_{br}, 1H, 1-H), 5.12 (d, J=3 Hz, 1H, 2-H), 7.14 (d, J=1 Hz, 1H, 5-H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=47.67 (C-7), 53.23 (C-10), 55.56 (C-2), 74.44 (C-1), 89.92 (C-6), 124.37 (C-4), 143.89 (C-5), 151.03 (C-8), 159.94 (C-9), 182.12 (C-3); the spectroscopic dates were taken from the spectra of the mixtures.

Diolbenzylamide 39. To a solution of acid **25** (15 mg, 0.044 mmol) in dry THF (3 ml) was added Staab's reagent (7 mg, 0.044 mmol, 1 equiv.) at room temperature. The solution was stirred for 10 min, then benzylamine (5 mg, 0.047 mmol, 1.1 equiv.) was added at room temperature. After stirring the reaction mixture for 1 h, it was worked up by purification by flash chromatography. In this way 7 mg (50%) of **39** were obtained as a brown oil; $[\alpha]_D^{20}$=71.5° (c=0.38, $CHCl_3$); IR ($CHCl_3$): ν=3580 cm^{-1} (w), 3504 (w), 3416 (m), 3064 (w), 3040 (w), 2928 (w), 1700 (s), 1680 (s), 1600 (m), 1528 (s), 1252 (m), 1128 (m), 1108 (m), 908 (m); ^1H NMR (400 MHz, $CDCl_3$): δ=3.23 (d, J=18 Hz, 1H, 7-H), 3.89 (d, J=18 Hz, 1H, 7-H), 4.21 (tr, J=2.5 Hz, 1H, 1-H), 4.54 (dd, J=2/6 Hz, 2H, 10-H), 4.63 (d, J=3 Hz, 1H, 2-H), 6.24 (d, J=10 Hz, 1H, 4-H), 6.59 (dd, J=2/10 Hz, 1H, 5-H), 6.98 (tr, J=6 Hz, 1H, NH), 7.27–7.39 (m, 5H, 12-H, 12′-H, 13-H, 13′-H, 14-H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=42.66 (C-10), 43.66 (C-7), 73.02 (C-1), 73.07 (C-2), 87.45 (C-6), 127.91 (C-14), 127.92 (C-13, C-13′), 128.87 (C-12, C-12′), 129.01 (C-4), 137.10 (C-11), 143.40 (C-5), 154.26 (C-8), 158.85 (C-9), 197.15 (C-3); MS (150°C): m/z (%)=316 (M^+, 6), 256 (3), 175 (15), 160 (6), 106 (71), 91 (100); HRMS: m/z for $C_{16}H_{16}N_2O_5$ calcd: 316.1059, found: 316.1057.

Bisamide 40. To a solution of acid **30b** (20 mg, 0.096 mmol, 3 equiv.) in DMSO (0.3 ml) was added Staab's reagent (16 mg, 0.096 mmol, 3 equiv.) at room temperature. The solution was stirred for 5 min, then a solution of α,α′-diamino-*p*-xylene (4.3 mg, 0.087 mmol, 1 equiv.) in DMSO (0.1 ml) was added at room temperature. After stirring the reaction mixture for 1.5 h, it was quenched with brine, extracted with ethyl acetate and dried ($MgSO_4$). Purification by flash chromatography yielded 5 mg (30%) of **40** as a white solid; $[\alpha]_D^{20}$=151.3° (c=0.21, $CHCl_3$); IR ($CHCl_3$): ν=3418 cm^{-1} (w), 2999 (w), 2928 (m), 1686 (s), 1601 (m), 1530 (m), 1259 (m), 1230 (m), 1015 (w), 830 (w); ^1H NMR (400 MHz, acetone-d_6): δ=3.55 (d, J=18 Hz, 1H, 7-H), 3.59 (dd, J=2/3.5 Hz, 1H, 1-H), 3.72 (d, J=18 Hz, 1H, 7-H), 4.00 (d, J=2.5/3.5 Hz, 1H, 2-H), 4.50 (d, J=6.5 Hz, 2H, 10-H), 6.08 (dd, J=2/10.5 Hz, 1H, 4-H), 6.80 (dd, J=2.5/10 Hz, 1H, 5-H), 7.34 (s, 2H, 12-H, 12′-H); ^{13}C NMR (100 MHz, actone-d_6): δ=43.31 (C-10), 44.50 (C-7), 54.17 (C-1), 58.06 (C-2), 83.77/83.78 (C-6), 128.20 (C-4), 128.74/128.75 (C-12, C-12′), 138.85/138.86 (C-11), 143.53 (C-5), 155.52 (C-8), 159.61 (C-9), 192.84 (C-3); FAB-MS: m/z (%)=541 (M+23, 10), 519 (M+1, 16), 460 (17), 413 (28), 392 (31), 391 (100), 329 (44), 307 (98), 289 (55), 259 (66), 241 (17).

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