Organic & Biomolecular Chemistry

PAPER

View Article Online
View Journal | View Issue

Cite this: *Org. Biomol. Chem.*, 2018, **16**, 7674

First enantioselective total synthesis of altersolanol A†

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Received 28th August 2018,
Accepted 28th September 2018

DOI: 10.1039/c8ob02113a

rsc.li/obc

The first enantioselective total synthesis of altersolanol A, a secondary metabolite from the endophytic fungi *Stemphylium globuliferum* and *Alternaria solani*, is described. The key step towards the tetrahydroanthraquinone core was an asymmetric *Diels–Alder* (D–A) cycloaddition promoted by (*R*)-3,3′-diphenyl-BINOL/boron Lewis acid with good to excellent yields and excellent diastereo- and enantioselectivity (>95 : 5 dr and 98 : 2 er).

Introduction

Many types of cancers have developed multi-resistance mechanisms for a suite of different drugs making it important to develop new alternatives.[1] Altersolanol A is a highly sought after member of the tetrahydroanthraquinone class of substrates. These species are known to be widely distributed as secondary metabolites in natural sources.[2,3] Representative analogues include the polyketide family of altersolanols (altersolanol A–C, **1–3**)[4–6] and alterporriols (alterporriol D, **4**)[5,7] (Fig. 1). These natural compounds were isolated from multiple endophytic fungi including *Stemphylium globuliferum*,[8] *Alternaria solani*[9] and *Alternaria porri*.[10] Altersolanol A is known to inhibit plant respiration[11] and exhibits cytotoxic activity against 34 human cancer cell lines.[12] In 1967 Stoessl *et al.* isolated altersolanol A for the first time from *Alternaria solani*. Two years later the relative configuration was elucidated,[9,13] and in 2012 the absolute configuration was determined by Kanamaru *et al.* using circular dichroism (CD) spectroscopy.[14]

It was shown that enantioselective D–A reactions represent a powerful transformation in organic chemistry with formation of two new σ-bonds and up to four adjacent stereogenic centers.[15–19] To the best of our knowledge, two reports on racemic total synthesis of altersolanols have been reported to date. Altersolanol B was prepared by Kelly and Montury in 1978[20] and altersolanol A was prepared by Krohn and coworkers in 1988.[21] Kelly used a boron-mediated D–A reaction of dienophile **5a** with an excess of diene **6a** to obtain **7** in 80% yield (Scheme 1, entry a). Alternatively, Krohn presented the D–A reaction of acetate dienophile **5d** and OTMS-protected diene **6b** to form **7** in 66% yield (Scheme 1, entry b). The start-

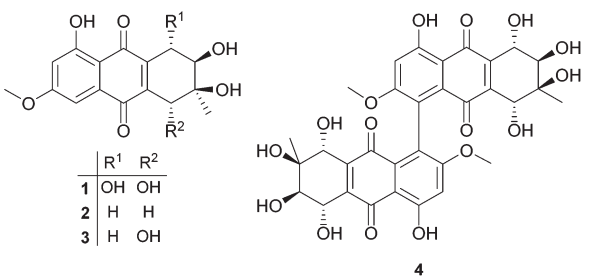
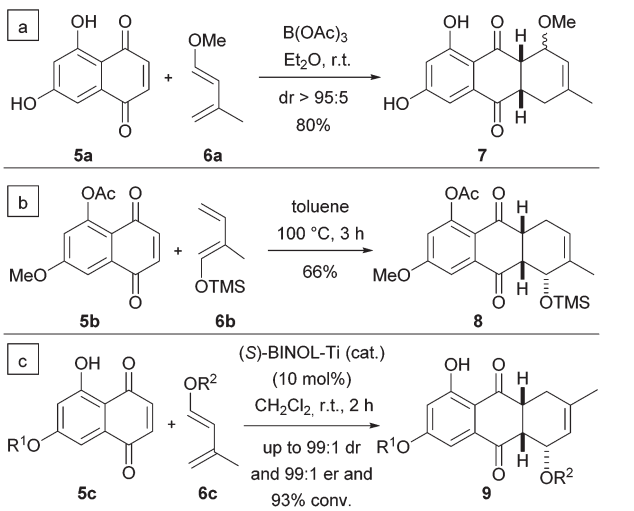


Fig. 1 Structure of altersolanol A–C (**1–3**) and alterporriol: D (**4**).



Scheme 1 Key reaction of racemic total synthesis of altersolanol A and B *via* a regioselective Diels–Alder reaction [by Kelly and Montury[20] (a) as well as the Krohn group[21] (b), and an investigation of Böse *et al.*[22] (c).

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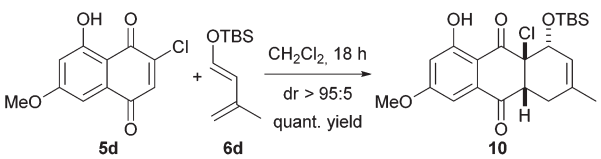
† Electronic supplementary information (ESI) available: Experimental details and spectra of all products. See DOI: 10.1039/c8ob02113a

ing point for the total synthesis of enantiomerically pure altersolanol A (**1**) consists of an enantioselective D–A reaction between juglone-based dienophiles **5c** and 1-oxygenated dienes **6c**. Product **9** was successfully accessed using a BINOL-Ti-derived catalyst first prepared by our group members Böse *et al.*[22] (Scheme 1, entry c). Herein we would like to present our enantioselective synthetic route towards altersolanol A (**1**) *via* a chiral Lewis acid promoted D–A reaction.

Results and discussion

Our total synthesis was initiated by preparing the chloro-substituted dienophile **5d** following procedures reported by Brassard *et al.*[23] and the Dallavalle group[24] (for detailed conditions see the ESI†). In contrast to the dienophiles **5a–c**, the halogen substituent showed a significant effect on the regioselectivity. In previous studies it was shown that the phenolic proton of the dienophiles functioned as a weak Lewis acid, but the additional electron-withdrawing effect of the halogen led to an enhanced regioselectivity of >95 : 5 dr.[25] However, previous literature focused only on the regioselectivity and subsequent aromatization steps where the chiral information is lost.[26,27] Another benefit of the herein presented dienophile **5d** is the basic workup that was sufficient to establish the benzoquinone core in quantitative yield, instead of oxidation procedures.[21] It was shown that *peri*-hydroxynaphthoquinones are attractive candidates for Lewis acid promotion because of the complex formation of the hydroxy group and the coordination of the carbonyl with highly diminishing conformational mobility. By using achiral or chiral Lewis acids regiocontrol could be influenced in a predictable manner.[20] Most importantly asymmetric induction should take place for this system as a result of the steric hindrance at one site of the quinone moiety.[28–30]

The study was initialized by investigating the cycloaddition between chloro-substituted naphthoquinone **5d** and 2.0 equiv. of OTBS-protected diene **6d**[22] (for detailed synthetic conditions see the ESI†) yielding racemic D–A product **10** (Scheme 2). As a first objective, we wanted to find a convenient purification protocol for the isolation of product **10**, because standard procedures (chromatography on silica gel) led to aromatisation, which is well documented.[31] However, upon treatment with *n*-pentane the excess of diene was extracted, while at the same time analytically pure D–A product **10** was formed as a precipitate. A 2D-NMR study verified that **10** was synthesised as a single constitutional isomer (Fig. 2). HMBC



Scheme 2 Racemic D–A reaction of dienophile **5d** with diene **6d** to D–A product **10**.

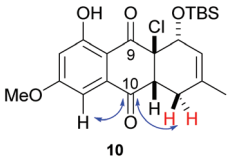
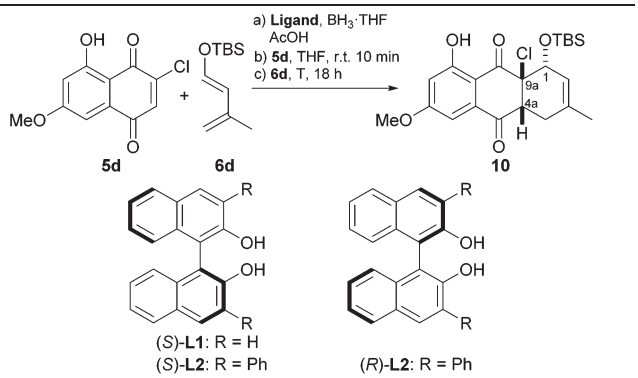


Fig. 2 HMBC-correlations showing the relative regioselectivity of D–A product **10** to aromatic protons and diastereotopic protons (red).

experiment and significant correlations of the carbonyl group (C-10) with the aromatic proton and the diastereotopic protons allowed an unambiguous assignment; D–A product **10** had full *endo*-selectivity, and no *exo*-product was detected.

Inspired by the asymmetric D–A reaction of juglone-based moieties,[28–30] our results of BINOL/boron Lewis acid promoted cycloaddition are presented in Table 1. At this point it is worth mentioning that water-free conditions were essential for the success of the reaction. The dark red colour of the complex from the chiral Lewis acid and dienophile confirmed that the reaction conditions were sufficiently dry. Another important observation is that complex formation between the dienophile and BINOL–boron reagent was complete within 10 min. However, no D–A product was formed over the course of an hour.[30] Using (*S*)-BINOL (*S*)-**L1** as a chiral ligand the cycloaddition in THF resulted in 80% yield, but in a moderate enantiomeric ratio of 33 : 67 of products (1*R*,4a*R*,9a*R*)-**10** and

Table 1 Screening of the chiral ligand for the asymmetric D–A reaction



Entry	Ligand	Equiv. (ligand)	*T* [°C]	Yield[a] [%]	er[b]
1	(*S*)-**L1**	2.0	22	80	33 : 67
2[c]	(*S*)-**L1**	2.0	22	94	36 : 64
3[d]	(*S*)-**L1**	2.0	22	41	28 : 72
4	(*S*)-**L1**	2.0	4	85	34 : 66
5[e]	(*S*)-**L2**	2.0	4	90	3 : 97
6[e]	(*R*)-**L2**	2.0	4	77	98 : 2
7[e]	(*R*)-**L2**	1.2	4	72	72 : 28
8[f,g]	(*R*)-**L2**	2.0	4	86	98 : 2

[a] Conditions: Chiral ligand, BH_3·THF, AcOH, dienophile **5d** (1.00 equiv., 0.10 mmol), diene **6d** (2.00 equiv.), isolated yield. [b] er = (1*R*,4a*R*,9aR)-**10**:(1*S*,4a*S*,9a*S*)-**10**, determined by chiral HPLC [Lux-Amylose (250 mm 46 mm, Fa. Phenomenex)]. [c] Reaction in toluene. [d] Reaction in CH_2Cl_2. [e] **5d** (0.05 mmol). [f] With the recycled ligand, one cycle, 98% recovery (*R*)-**L2**. [g] **5d** (0.63 mmol).

(1*S*,4a*S*,9a*S*)-**10** (Table 1, entry 1). We next changed the solvent to toluene and increased the yield, but a comparable enantiomeric ratio was obtained (Table 1, entry 2). Using dichloromethane as a solvent, the yield dropped significantly to 41%. A slightly better enantiomeric ratio of 28 : 72 was observed (Table 1, entry 3). For the next optimisation, we used THF as a solvent, because of reaction handling. The temperature was lowered to 4 °C, but no improvement with ligand (*S*)-**L1** was observed (Table 1, entry 4).

Employing the bulkier ligand (*S*)-**L2** afforded excellent selectivity of product (1*S*,4a*S*,9a*S*)-**10** with an enantiomeric ratio of 3 : 97 and a yield of 90% (Table 1, entry 5). According to Kelly and co-workers (*S*)-diphenyl-BINOL (*S*)-**L2** favours the formation of the (*S*)-configuration at C-1, which was determined during the synthesis of (−)-bostrycin.[28,32] With the potential catalyst and the optimised reaction conditions we had to use the (*R*)-**L2** ligand to selectively prepare the (*R*)-configured D–A product **10** (at C-1).[14] Herein we expected that complex **11** was formed under water-free conditions with the upper side being blocked by the phenyl residue. As a result, for the D–A reaction with *endo*-selectivity the diene **6d** had to approach the complexed dienophile **11** from the lower face (Fig. 3). Ligand (*R*)-**L2** was synthesised on a 10 g scale according to a previously reported procedure[33,34] (for detailed conditions see the ESI†). The asymmetric D–A product (1*R*,4a*R*,9a*R*)-**10** was prepared in 77% yield and with an excellent enantiomeric ratio of 98 : 2 (Table 1, entry 6). When the amount of chiral BINOL–boron reagent was reduced to 1.2 equiv., the enantiomeric ratio decreased dramatically (Table 1, entry 7).[30] Finally, it should be noted that recycled ligand (*R*)-**L2** yielded in a subsequent reaction 86% of (1*R*,4a*R*,9a*R*)-**10** in an enantiomeric ratio of 98 : 2 (Table 1, entry 8).

The next step was the epoxidation of (1*R*,4a*R*,9aR)-**10** and the conversion to TBS-protected diol (1*S*,2*S*)-**14** (Scheme 3). Due to the instability of compound **10** upon common workup methods, the epoxidation was attempted first without further purification of the intermediate. However, no conversion towards epoxide **12** was observed. As a result, it was necessary to purify product **10** utilizing a water-cooled flash-chromatography system. Subsequently, epoxide **12** was obtained in a diastereomeric ratio of 5.5 : 1 after 4 d, and basic aqueous NaOH washes led to the elimination product **13** in quantitative yield.

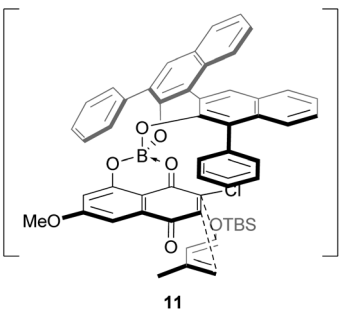
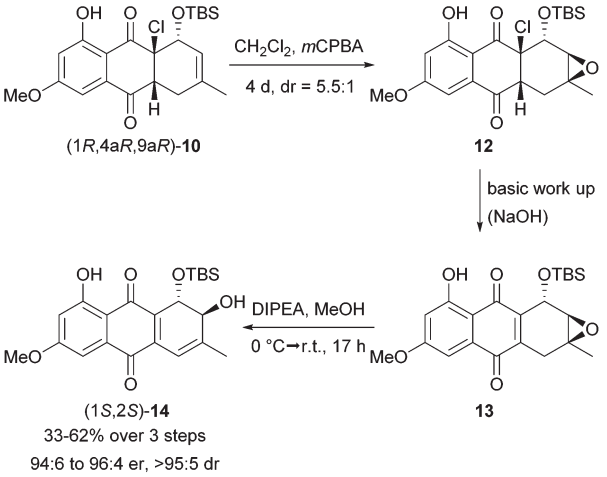


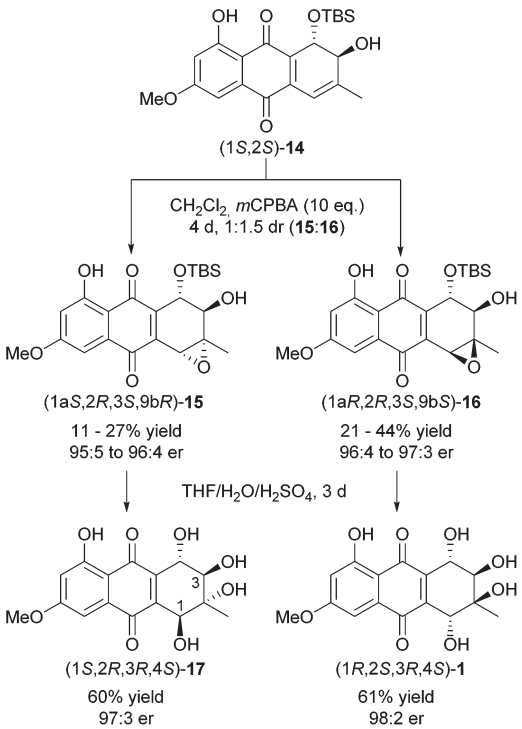
Fig. 3 Demonstration of the intermediacy of the Lewis acid complex with dienophile **5d** and diene **6d** in the *endo*-transition state.



Scheme 3 Reaction scheme for the synthesis of OTBS-protected diol (1*S*,2*S*)-**14**.

The epoxide was then opened with the sterically hindered base diisopropylethylamine (DIPEA). This produced the allyl alcohol (1*S*,2*S*)-**14** in 33–62% yield over three steps with excellent enantiomeric ratios of 94 : 6 to 96 : 4 and >95 : 5 dr. Mono-OTBS-protected *cis*-diol was not observed, likely due to its aromatisation under basic conditions.

In the next step towards the total synthesis of altersolanol A (**1**), the allyl alcohol double bond of (1*S*,2*S*)-**14** was epoxidized (Scheme 4). Treatment of **14** with *m*CPBA led to separable diastereoisomers (1a*R*,2*R*,3*S*,9b*S*)-**15** and(1a*S*,2*R*,3*S*,9b*R*)-**16** in



Scheme 4 Epoxidation and epoxide opening to (1*S*,2*R*,3*R*,4*S*)-**17** and altersolanol A (**1**).

yields from 32 to 71% with a diastereomeric ratio of 1 : 1.5 (**15** : **16**) (for further epoxidation experiments see the ESI†).

First epoxide **15** was opened under aqueous acidic conditions. Herein we found that the epoxide was opened with high regioselectivity at the allylic position through a *trans*-diaxial addition of water. The all-*trans* product **17** was obtained in 60% yield and 97 : 3 er. We could identify a diagnostic long-range coupling constant of 1.3 Hz for 1- and 3-H (W-coupling), which shows the *cis*-relationship of these protons. The spectral data were identical to those published by Krohn *et al.*[21] Finally, altersolanol A (**1**) was obtained in 61% yield with an enantiomeric ratio of 98 : 2 after the hydrolytic ring opening of epoxide **16**. The correct classification of epoxide opening for **1** was confirmed unambiguously with an authentic sample of the natural product[35] and the analytics were in agreement with literature values.[14,36]

Conclusions

In summary, we have successfully presented a new synthetic strategy for altersolanol A and its first enantioselective total synthesis. The key element of the synthesis was the asymmetric D–A cycloaddition promoted by the BINOL/boron Lewis acid complex in high yield with >95 : 5 dr and 98 : 2 er. Next the consecutive synthetic route was used towards *trans*-diol **14** in 62% yield over four steps. The additional epoxidation led to two diastereomers in a total yield of 71%, in which we could determine the absolute configuration. In the last step, aqueous acidic conditions led to epoxide opening and altersolanol A (**1**) and its all-*trans* derivative **17** were obtained with high enantiomeric ratios of 98 : 2 and 97 : 3, respectively. Indirectly, we thus also proved the assumed stereochemical outcome of the D–A reaction. The determination of the physiological data from the synthesised products is in progress.

Experimental

Experimental procedures and characterization data for compounds **5d**, **6d** and (*R*)-**L2** are provided in the ESI.†

General information

Unless specified, the reactions were carried out by the standard *Schlenk*-technique under dry Ar/N_2 and magnetic stirring. All reagents were used as purchased from commercial suppliers without further purification. Glassware was oven-dried at 120 °C overnight. Solvents were dried and purified by conventional methods prior to use. THF and dichloromethane were used directly from an MB SPS-800 (M Braun). Solvents for chromatography (petroleum ether, ethyl acetate, dichloromethane and methanol) were distilled prior to use. Column chromatography was performed on silica gel 60, 0.040–0.063 nm (230–400 mesh). Thin layer chromatography (TLC) was performed on silica gel POLY-GRAM® SIL G/U254 plates (Macherey-Nagel) and was visualized with UV light (254/366 nm UV-lamp) and cerium-molybdate-solution [10 g $Ce(SO_4)_2 \cdot 4\ H_2O$, 25 g phosphomolybdic acid, 60 mL conc. H_2SO_4, 940 mL H_2O]. Preparative TLC was performed on precoated TLC plates SIL G-100 UV_{254} (20 cm × 20 cm) (Macherey-Nagel). NMR spectra were recorded on a Bruker Advance DRX/600 spectrometer. ^{1}H-NMR analysis was performed at 600 MHz and ^{13}C-NMR spectra were proton decoupled at 151 MHz. Chemical shifts are reported in ppm relative to residual solvent signals ($CDCl_3$: 7.26 ppm for ^{1}H-NMR and 77.16 ppm for ^{13}C-NMR, DMSO-d_6: 2.50 ppm for ^{1}H-NMR and 39.52 ppm for ^{13}C-NMR, MeOD-d_4: 3.31 ppm for 1H-NMR and 49.0 ppm for^{13}C-NMR). The multiplicity in NMR spectra is given in the following abbreviations: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet. The enantiomeric excess of the products was determined by HPLC (DIONEX GmbH, Chiralcel ODH, Chiralpak IA, Chiralpak IB, Chiralpak IC columns, flow 0.5 mL min^{-1}, 25 °C). High resolution mass spectra were recorded by FT-IR-MS using electrospray ionization (ESI^+) (Applied Biosystems/MDS SCIEXQ Model Trap 4000). Infrared data were recorded on a *PerkinElmer SpectrumOne* instrument and *PerkinElmer SpectrumTwo* instrument as neat samples. Melting points were measured on a *Büchi Melting Point B-540* instrument. Optical rotations were recorded on an *A. Krüss Optronic* P8000 polarimeter.

Activation of molecular sieves

The success of the asymmetric *Diels–Alder* reaction of dienophile **5d** and diene **6d** promoted by (*R*)-**L2**, borane-THF complex and glacial acetic acid is dependent on the activation of 3 Å molecular sieves and the use of fresh, nitrogen flushed glacial acetic acid.

The 3 Å molecular sieves were used directly at room temperature without pre-drying in an oven. We used about 20 g of 3 Å molecular sieves (Carl Roth, molecular sieves 3 Å, 0.3 nm, type 564, pearls, ø1.6–2.5 mm) for 250 mL of THF, and 3.5 g of 3 Å molecular sieves for 10 mL of glacial acetic acid. First the 3 Å molecular sieves were placed in a 250 mL flask, which was heated to 450 °C with a heat gun for 15 min under high vacuum (10^{-3} mbar). Further activation at 250 °C overnight under high vacuum (10^{-3} mbar) was performed. After heating for 18 h dry and degassed THF was obtained from the solvent purification system [MB SPS-800 (M Braun)] and fresh glacial acetic acid was transferred into the flasks with activated 3 Å molecular sieves under an atmosphere of dry argon. To our knowledge, storage of both solvents over sieves for 48 h produced the optimal solvent dryness, which resulted in the best enantiomeric control for the asymmetric *Diels–Alder* reaction. One major problem was the use of glacial acetic acid, because of its high hygroscopicity. A new bottle of glacial acetic acid was used two to three times after opening (no more than two weeks after opening), otherwise the enantiomeric excess of the *Diels–Alder* product dropped dramatically to 40 to 60% ee.

(1*R*,4a*R*,9a*R*)-1-((*tert*.Butyldimethylsilyl)oxy)-9a-chloro-8-hydroxy-6-methoxy-3-methyl-1,4,4a,9a-tetrahydroanthracene-9,10-dione (10)

Following the "*activation of molecular sieves*" THF and glacial acetic acid were prepared. In a 100 mL *Schlenk*-tube (*R*)-**L2**

(551 mg, 1.26 mmol) was dissolved in THF (25 mL). Subsequently, a solution of 1 M BH_3·THF complex (1.26 mL, 1.26 mmol) and glacial acetic acid (87.3 μl, 1.26 mmol) was added *via* a *Hamilton* syringe and a strong gas formation was observed. The reaction mixture was stirred for 1 h at room temperature, and the solvent was evaporated under inert conditions with a high-vacuum Schlenk line at minimum 50–100 mbar. The Schlenk tube was evaporated under high vacuum (10^{-3} mbar) for 1 h and a white foam/solid could be observed [note: no colourless oil should remain in the *Schlenk* tube (no water-free conditions)]. Gentle heating at 80–100 °C can help evaporate any residual THF). The white residue was dissolved in THF (25 mL) and a solution of dienophile **5d** (150 mg, 0.63 mmol) in THF (12.5 mL) was added and stirring was implemented for 10 min at room temperature (dark red solution). The reaction mixture was cooled with an external ice bath and diene **6d** (249 mg, 1.26 mmol) was added in one portion. After 1 min a decolourization to bright orange/red was observed and the reaction was stirred for an additional 18 h at 4 °C. After observing full conversion *via* TLC analysis water (50 μl) was added and the solvent was evaporated under reduced pressure. The product was purified *via* column chromatography (PE : EE = 90 : 10) and could be isolated as a light-yellow oil (261 mg, 95%, 98 : 2 er).

It must be noted that the *Diels–Alder* product is a colourless solid, but is not stable under chromatography conditions, and that elimination of HCl to the benzoquinone core can occur (yellowish product). Also, (*R*)-**L2** was recovered in 95–99% yield.

R_f = 0.4 (PE : EE = 90 : 10); mp 76 °C (in PE); δH (600 MHz, $CDCl_3$) −0.30, 0.12 (2 × s, 2 × 3H, $Si(CH_3)_2$), 0.47 (s, 9H, $SiC(CH_3)_3$), 1.85 (br s, 3H, 2-CH_3), 2.33 (ddq, $^2J_{4Ha,4Hb}$ 18.4 Hz, $^3J_{4Ha,4a}$ 6.7 Hz, $^3J_{4Ha,3\text{-}Me}$ 1.1 Hz, 1H, 4-H_a), 3.07 (ddd, $^2J_{4Hb,4Ha}$ 18.4 Hz, $^3J_{4Hb,3\text{-}Me}$ 2.3 Hz, $^3J_{4Hb,4a}$ 0.9 Hz, 1H, 4-H_b), 3.49 (ddd, $^3J_{4a,4Ha}$ 6.8 Hz, $^3J_{4a,4Hb}$ 0.9 Hz 1H, $^4J_{4a,1}$ 0.9 Hz 1H, 4a-H), 3.88 (s, 3H, OCH_3), 4.34 (dd, $^3J_{1,2}$ 5.1 Hz, $^4J_{1,4a}$ 0.9 Hz, 1H, 1-H), 5.45 (dd, $^3J_{2,1}$ 5.1 Hz, $^4J_{1,4a}$ 0.9 Hz, 1H, 2-H), 6.62 (d, $^4J_{7,5}$ 2.5 Hz, 1H, 7-H), 7.02 (d, $^4J_{5,7}$ 2.5 Hz, 1H, 5-H), 12.28 (s, 1H, 8-OH) ppm; δC (151 MHz, $CDCl_3$) −5.4, −4.7 ($Si(CH_3)_2$), 17.6 (SiC), 23.5 (2-CH_3), 25.2 ($SiC(CH_3)_3$), 25.7 (C-4), 52.1 (C-4a), 56.2 (OCH_3), 72.1 (C-1), 72.5 (C-3), 105.5 (C-7), 105.8 (C-5), 113.1 (C-8a), 119.2 (C-2), 136.6 (C-9a), 139.2 (C-10a), 165.1 (C-8), 166.6 (C-6), 191.5 (C-10), 197.6 (C-9) ppm; ν_{max}/cm^{-1} 2928, 2853, 1713, 1677, 1636, 1612, 1568, 1496, 1477, 1429, 1413, 1382, 1359, 1342, 1293, 1257, 1243, 1220, 1191, 1122, 1100, 1054, 1041, 1006, 958, 942, 909, 879, 858, 846, 823, 787, 772, 749, 719, 691, 662; HRMS (ESI, positive-ion): calc.: 437.1551 ($C_{22}H_{30}O_5ClSi$) [$(M + H)^+$] found: 437.1547; HPLC: column: Lux-Amylose (250 mm ·46 mm, Fa. Phenomenex); solvent: heptane/2-propanol = 99 : 1; flowrate: 0.5 mL min^{-1}, detection: 245 nm; t_R [(1*S*,4a*S*,9a*S*)-**10**] 13.9 min; t_R [(1*R*,4a*R*,9a*R*)-**10**] 14.8 min.

(1*S*,2*S*)-1-((*tert*.Butyldimethylsilyl)oxy)-2,8-dihydroxy-6-methoxy-3-methyl-1,2-dihydroanthracene-9,10-dione (14)

In a 25 mL *Schlenk*-tube (1*R*,4a*R*,9a*R*)-**10** (119 mg, 0.27 mmol) was dissolved in CH_2Cl_2 (8 mL) and *m*CPBA (72%, 389 mg, 1.64 mmol) was added to the stirring reaction mixture. The reaction was then allowed to continue stirring at room temperature for 4 days. ^{1}H-NMR has been used to monitor the reaction and the phenolic proton was detected as the reference signal (chemical shift from 12.28 ppm to 12.11 ppm and 12.21 ppm (ratio 1 : 5.5)). Afterwards the reaction mixture was diluted with CH_2Cl_2 (100 mL) and the organic phase was washed with 1 M NaOH (6 × 25 ml), 2 M NaOH (6 × 25 mL) and brine (1 × 25 mL). The organic layer was dried with $MgSO_4$ and filtered and the solvent was evaporated under vacuum. The elimination of HCl was determined by ^{1}H-NMR (chemical shift from 12.11 ppm to 12.30 ppm, no chemical shift of signal at 12.21 ppm). Elimination product **13** was isolated as a red oil in 43% to quantitative yield and was used without further purification. The NMR-spectra of elimination product **13** are given as a reference.

δH (600 MHz, $CDCl_3$) 0.11, 0.27 (2 × s, 2 × 3H, $Si(CH_3)_2$), 0.87 (s, 9H, $SiC(CH_3)_3$), 1.54 (s, 3H, 3-CH_3), 2.70–2.75 (m, 1H, 4-H_a), 3.18–3.19 (m, 1H, 2-H), 3.25–3.30 (m, 1H, 4-H_b), 3.89 (s, 3H, OCH_3), 5.40 (br s, 1H, 1-H), 6.64 (d, $^4J_{7,5}$ 2.5 Hz, 1H, 7-H), 7.16 (d, $^4J_{5,7}$ 2.5 Hz, 1H, 5-H), 12.30 (s, 1H, 8-OH) ppm; δC (151 MHz, $CDCl_3$) = −4.7, −4.3 ($Si(CH_3)_2$), 18.3 (SiC), 22.3 (3-CH_3), 25.9 ($SiC(CH_3)_3$), 28.5 (C-4), 55.5 (C-3), 56.2 (OCH_3), 60.3 (C-3), 62.2 (C-1), 106.5 (C-7), 107.7 (C-5), 109.6 (C-8a), 133.5 (C-10a), 140.2 (C-4a), 141.1 (C-9a), 164.3 (C-8), 166.0 (C-6), 184.5 (C-10), 187.2 (C-9) ppm.

In a *Schlenk* flask the elimination product **13** (112 mg, 0.27 mmol) was dissolved in methanol (15 mL). The solution was cooled to 0 °C and diisopropylethylamine (0.18 mL, 1.08 mmol) was added *via* a syringe and stirred for 3 h at 0 °C. Then the reaction mixture was warmed to room temperature and stirred for an additional 16 h. The solution was diluted with ethyl acetate (50 mL) and saturated NH_4Cl solution (50 mL) and then evaporated under reduced pressure to a total volume of 75 mL. It was observed that direct evaporation of methanol under vacuum had led to decomposition because of basic conditions. The layers were separated and the aqueous layer was extracted with ethyl acetate (1 × 25 mL). The combined organic layers were washed with saturated NH_4Cl (4 × 25 mL), dried with $MgSO_4$, and filtered and the solvent was removed under reduced pressure. The crude product has to be purified immediately *via* column chromatography and preparative TLC (CH_2Cl_2 : MeOH = 98 : 2) because of decomposition. The OTBS-protected diol **14** was isolated as a red solid (46.1 mg, 41%, 96 : 4 er, over four steps).

R_f = 0.6 (CH_2Cl_2 : MeOH = 98 : 2); mp 59–61 °C (in CH_2Cl_2); $[\alpha]_D^{20}$ −46.8 (c 0.50 in $CHCl_3$); δH (600 MHz, $CDCl_3$) 0.05, 0.25 (2 × s, 2 × 3H, $Si(CH_3)_2$), 0.81 (s, 9H, $SiC(CH_3)_3$), 1.60 (d, $^3J_{2\text{-}OH,2}$ 7.9 Hz, 3H, 2-OH), 2.16 (d, $^4J_{3\text{-}Me,4}$ 1.6 Hz, 3H, 3-CH_3), 3.89 (s, 3H, OCH_3), 3.99 (dd, $^3J_{2,2\text{-}OH}$ 7.7 Hz, $^3J_{2,1}$ 1.6 Hz, 1H, 2-H), 5.03 (d, $^3J_{1,2}$ 1.6 Hz 1H, 1-H), 6.63 (d, $^4J_{7,5}$ 2.5 Hz, 1H, 7-H), 6.69 (q, $^4J_{4,3\text{-}Me}$ 1.6 Hz, 1H, 4-H), 7.15 (d, $^4J_{5,7}$ 2.5 Hz, 1H, 5-H), 12.49 (s, 1H, 8-OH) ppm; δC (151 MHz, $CDCl_3$) −4.7, −4.2 ($Si(CH_3)_2$), 18.1 (SiC), 22.6 (3-CH_3), 25.9 ($SiC(CH_3)_3$), 56.1 (OCH_3), 65.5 (C-1), 72.7 (C-2), 106.6 (C-7), 107.8 (C-5), 110.0 (C-8a), 115.7 (C-4), 133.4 (C-10a), 135.6 (C-9a), 137.4 (C-4a),

146.7 (C-3), 164.1 (C-8), 165.8 (C-6), 183.5 (C-10), 187.8 (C-9) ppm; ν_{max}/cm^{-1} 3472, 2954, 2929, 2894, 2855, 1672, 1652, 1616, 1584, 1442, 1386, 1354, 1303, 1257, 1207, 1162, 1073, 1013, 956, 864, 836, 776, 676, 630, 591, 526, 471; HRMS (ESI, positive-ion): calc.: 417.1733 ($C_{22}H_{28}O_6Si$) [(M + H)$^+$] found: 417.1724, HPLC column: Lux-Amylose (250 mm 46 mm, Fa. Phenomenex); solvent: heptane/2-propanol = 90 : 10; flowrate: 0.5 mL min^{-1}, detection: 225 nm; t_R [(1*S*,2*S*)-**14**] 16.3 min; t_R [(1*R*,2*R*)-**14**] 22.7 min.

(1a*S*,2*R*,3*S*,9b*R*)-3-((*tert*.Butyldimethylsilyl)oxy)-2,5-dihydroxy-7-methoxy-1a-methyl-1a,2,3,9b-tetrahydroanthra[1,2-*b*]oxirene-4,9-dione (15)

In a 50 ml *Schlenk* flask a solution of TBS-protected diol (1*S*,2*S*)-**14** (114.8 mg, 0.28 mmol) was dissolved in CH_2Cl_2 (24 mL) under a nitrogen atmosphere and *m*CPBA (72%, 661 mg, 2.76 mmol) was added. The reaction mixture was stirred for 4 d and the progress was monitored using ^{1}H-NMR analysis. The diastereomeric ratio was determined by ^{1}H-NMR (1 : 1.5, **15** : **16**). The solution was extracted with 10% (w/w) Na_2SO_3 solution (1 × 20 mL) and saturated $NaHCO_3$ solution (1 × 20 mL), the organic layer was dried with $MgSO_4$ and filtered and the solvent was evaporated. The crude product was purified by column chromatography (PE : EE = 80 : 20). Epoxide (1a*S*,2*R*,3*S*,9b*R*)-**15** was isolated as a yellow solid (32.2 mg, 27%, 96 : 4 er).

R_f = 0.3 (PE : EE = 80 : 20), mp 88 °C (in PE); $[\alpha]_D^{20}$ +52.2 (c 0.50 in $CHCl_3$); δH (600 MHz, $CDCl_3$) 0.06, 0.26 (2 × s, 2 × 3H, $Si(CH_3)_2$), 0.88 (s, 9H, $SiC(CH_3)_3$), 1.67 (s, 3H, 1a-CH_3), 1.84 (d, $^3J_{2\text{-OH},2}$ 6.3 Hz, 1H, 3-OH), 3.91 (s, 3H, OCH_3), 4.13 (s, 1H, 9b-H), 4.13–4.14 (m, 1H, 2-H), 5.00 (d, $^3J_{3,2}$ 1.8 Hz, 1H, 3-H), 6.65 (d, $^4J_{6,8}$ 2.5 Hz, 1H, 6-H), 7.21 (d, $^4J_{8,6}$ 2.5 Hz, 1H, 8-H), 12.28 (s, 1H, 5-OH) ppm; δC (151 MHz, $CDCl_3$) −4.8, −4.1 ($Si(CH_3)_2$), 18.1 (SiC), 19.1 (1a-CH_3), 25.9 ($SiC(CH_3)_3$), 49.4 (C-9b), 56.2 (OCH_3), 64.0 (C-1a), 66.5 (C-3), 72.2 (C-2), 106.6 (C-6), 108.1 (C-8), 109.8 (C-4a), 133.5 (C-8a), 141.7 (C-9a), 142.2 (C-3a), 164.5 (C-5), 166.2 (C-7), 183.6 (C-9), 187.0 (C-4) ppm; ν_{max}/cm^{-1} 3506, 2951, 2930, 2891, 2857, 1667, 1640, 1614, 1575, 1491, 1463, 1443, 1388, 1305, 1259, 1207, 1163, 1101, 1078, 1048, 955, 863, 840, 777, 734, 701, 675; HRMS (ESI, positive-ion): calc.: 417.1683 ($C_{22}H_{29}O_7Si$) [(M + H)$^+$] found: 417.1680; HPLC column: Lux-Amylose (250 mm 46 mm, Fa. Phenomenex); solvent: heptane/2-propanol = 90 : 10; flowrate: 0.5 mL min^{-1}, detection: 220 nm; t_R [(1*S*,2*R*,3*S*,9b*R*)-**16**] 16.7 min; t_R [(1*R*,2*S*,3*R*,9b*S*)-**16**] 20.4 min.

(1a*R*,2*R*,3*S*,9b*S*)-3-((*tert*.Butyldimethylsilyl)oxy)-2,5-dihydroxy-7-methoxy-1a-methyl-1a,2,3,9b-tetrahydroanthra[1,2-*b*]oxirene-4,9-dione (16)

Epoxide (1a*R*,2*R*,3*S*,9b*S*)-**16** was obtained as a yellow solid (52.9 mg, 44%, 97 : 3 er) from the more polar fraction.

R_f = 0.6 (PE : EE = 80 : 20); mp 152 °C (in PE); $[\alpha]_D^{20}$ −200 (c 0.50 in $CHCl_3$); δH (600 MHz, $CDCl_3$) 0.03, 0.23 (2 × s, 2 × 3H, $Si(CH_3)_2$), 0.85 (s, 9H, $SiC(CH_3)_3$), 1.68 (s, 3H, 1a-CH_3), 2.36 (d, $^3J_{2\text{-OH},2}$ 7.2 Hz, 1H, 2-OH), 3.92 (s, 3H, OCH_3), 4.03 (s, 1H, 9b-H), 4.04 (d, $^3J_{2,2\text{-OH}}$ 7.2 Hz, $^4J_{2,3}$ 3.3 Hz, 1H, 2-H), 4.89 (d, $^3J_{3,2}$ 3.3 Hz, 1H, 3-H), 6.68 (d, $^4J_{6,8}$ 2.5 Hz, 1H, 6-H), 7.24 (d, $^4J_{8,6}$ 2.5 Hz, 1H, 8-H), 12.24 (s, 1H, 5-OH) ppm; δC (151 MHz, $CDCl_3$) −4.9, −4.5 ($Si(CH_3)_2$), 18.2 (SiC), 22.8 (1a-CH_3), 25.8 ($SiC(CH_3)_3$), 52.9 (C-9b), 56.3 (OCH_3), 59.4 (C-1a), 64.5 (C-3), 70.5 (C-2), 106.6 (C-6), 108.3 (C-8), 109.8 (C-4a), 133.3 (C-8a), 139.8 (C-9a), 146.0 (C-3a), 164.8 (C-5), 166.4 (C-7), 183.6 (C-9), 186.8 (C-4) ppm; ν_{max}/cm^{-1} 3505, 2929, 2856, 1737, 1643, 1616, 1570, 1494, 1462, 1371, 1318, 1253, 1196, 1159, 1075, 1059, 1040, 1004, 953, 858, 835, 779, 734, 707, 670, HRMS (ESI, positiv-ion): calc.: 417.1683 ($C_{22}H_{29}O_7Si$) [(M + H)$^+$] found: 417.1680, HPLC column: Lux-Amylose (250 mm 46 mm, Fa. Phenomenex); solvent: heptane/2-propanol = 90 : 10; flowrate: 0.5 mL min^{-1}, detection: 220 nm; t_R [(1*R*,2*R*,3*S*,9b*S*)-**16**] 16.3 min; t_R [(1*S*,2*S*,3*R*,9b*R*)-**16**] 22.7 min.

(1*S*,2*R*,3*R*,4*S*)-1,2,3,4,5-Pentahydroxy-7-methoxy-2-methyl-1,2,3,4-tetrahydroanthracene-9,10-dione (17)

In a 25 mL *Schlenk* flask epoxide (1*S*,2*R*,3*S*,9b*R*)-**15** (22.8 mg, 52.7 μmol) was dissolved in THF (6.6 mL) and H_2O (4.6 mL) and conc. H_2SO_4 (200 μL) was added. The reaction mixture was stirred for 3 days at room temperature and the reaction was monitored using TLC. After full conversion the reaction mixture was diluted with water (25 mL) and neutralized with saturated $NaHCO_3$ (8.5 mL). The aqueous solution was extracted with ethyl acetate (4 × 25 mL), dried with $MgSO_4$, and filtered and the solvent was evaporated. The crude product was first purified by preparative TLC (CH_2Cl_2 : MeOH = 90 : 10) and the product was isolated as a red solid (10.7 mg, 60%). After additional purification with RP-HPLC 4.8 mg of (1*S*,2*R*,3*R*,4*S*)-**17** was obtained. The spectroscopic data are in agreement with previously reported literature values.[21]

R_f = 0.5 (CH_2Cl_2 : MeOH = 90 : 10); mp 190 °C (in CH_2Cl_2); $[\alpha]_D^{22}$ −153 (c 0.12 in EtOH); δH (600 MHz, DMSO-d_6) 1.44 (s, 3H, 2-CH_3), 3.73 (ddd, $^3J_{3,3OH}$ 5.1 Hz, $^3J_{3,4}$ 2.3 Hz, $^4J_{3,1}$ 1.3 Hz, 1H, 3-H), 3.92 (s, 3H, OCH_3), 4.35 (dd, $^3J_{1,1OH}$ 9.1 Hz, $^4J_{1,3}$ 1.3 Hz, 1H, 1-H), 4.66 (dd, $^3J_{4,4OH}$ 8.9 Hz, $^3J_{4,3}$ 2.3 Hz, 1H, 4-H), 4.70 (d, $^3J_{3,4}$ 7.5 Hz, 1H, 1-OH), 4.93 (d, $^3J_{4OH,4}$ 8.9 Hz, 1H, 4-OH), 5.44 (s, 1H, 2-OH), 5.58 (d, $^3J_{3OH,3}$ 5.1 Hz, 1H, 3-OH), 6.87 (d, $^4J_{6,8}$ 2.5 Hz, 1H, 6-H), 7.07 (d, $^4J_{8,6}$ 2.5 Hz, 1H, 8-H), 12.26 (s, 1H, 5-OH) ppm; δC (151 MHz, DMSO-d_6) 23.3 (2-CH_3), 56.4 (OCH_3), 66.7 (C-4), 67.6 (C-1), 70.4 (C-2), 73.6 (C-3), 106.1 (C-6), 107.0 (C-8), 109.3 (C-10a), 133.4 (C-8a), 140.4 (C-4a), 142.6 (C-9a), 163.4 (C-5), 165.7 (C-7), 183.7 (C-9), 188.1 (C-10) ppm; ν_{max}/cm^{-1} 3354, 2940, 1665, 1644, 1607, 1489, 1437, 1387, 1301, 1261, 1204, 1141, 1050, 1025, 1000, 965, 933, 856, 782, 722, 638, 635, 610, 557, 532. HRMS (ESI, positive-ion): calc.: 337.0923 ($C_{16}H_{17}O_8$) [(M + H)$^+$] found: 337.0923; HPLC column: Chiralpak IA (250 mm 46 mm, Fa. Daicel); solvent: heptane/2-propanol = 70 : 30; flow rate: 0.5 mL min^{-1}, detection: 220 nm; t_R [(1*S*,2*R*,3*R*,4*S*)-**17**] 13.0 min; t_R [(1*R*,2*S*,3*S*,4*R*)-**17**] 33.9 min; RP-HPLC column: HyperClone (5 μm ODS (C18) 120 Å, LC Column 125 mm 4 mm, Fa. Phenomenex); solvent: H_2O : MeOH = 90 : 10 for 5 min, changed linearly to H_2O : MeOH = 40 : 60 (5–39 min) and to H_2O : MeOH = 0 : 100 (39–40 min), kept for 10 min (40–50 min) and changed linearly to H_2O : MeOH = 90 : 10 (50–51 min) and returned to the initial

conditions within 19 min; flow rate: 5 ml min^{-1}; detection 220 nm; t_R = 35 min.

(1*R*,2*S*,3*R*,4*S*)-1,2,3,4,5-Pentahydroxy-7-methoxy-2-methyl-1,2,3,4-tetrahydroanthracene-9,10-dione (altersolanol A) (1)

In a 25 mL *Schlenk* flask epoxide (1*R*,2*R*,3*S*,9b*S*)-**16** (28.1 mg, 65.0 mmol) was dissolved in THF (10 mL) and H_2O (7 mL) and conc. H_2SO_4 (300 μL) was added. The reaction mixture was stirred for an additional 3 days at room temperature. The reaction was monitored using TLC and after full conversion the reaction mixture was diluted with water (25 mL) and neutralized with saturated $NaHCO_3$ (12.5 mL). The aqueous solution was extracted with ethyl acetate (4 × 25 mL), dried with $MgSO_4$, and filtered and the solvent was evaporated. The crude product was first purified by preparative TLC (CH_2Cl_2 : MeOH = 90 : 10) and the product **1** was isolated as a red solid (13.3 mg, 61%, 98 : 2 er). After additional purification *via* reversed-phase HPLC 8 mg of altersolanol A was obtained. The spectroscopic data are in agreement with previously reported literature values.[14]

R_f = 0.4 (CH_2Cl_2 : MeOH = 90 : 10); mp 212 °C (in CH_2Cl_2); $[\alpha]_D^{20}$ −152 (c 0.10 in EtOH).[36] δH (600 MHz, MeOD-d_4) 1.44 (s, 3H, 2-CH_3), 3.85 (d, $^3J_{3,4}$ 7.5 Hz, 1H, 3-H), 3.92 (s, 3H, OCH_3), 4.52 (s, 1H, 1-H), 4.74 (d, $^3J_{4,3}$ 7.5 Hz, 1H, 4-H), 6.73 (d, $^4J_{6,8}$ 2.4 Hz, 1H, 6-H), 7.14 (d, $^4J_{8,6}$ 2.5 Hz, 1H, 8-H) ppm; δC (151 MHz, MeOD-d_4) 22.3 (2-CH_3), 56.7 (OCH_3), 70.3 (C-1), 70.7 (C-3), 74.6 (C-2), 75.3 (C-4), 106.8 (C-6), 108.5 (C-8), 111.1 (C-10a), 135.0 (C-8a), 143.4 (C-4a), 145.0 (C-9a), 165.6 (C-5), 167.7 (C-7), 185.0 (C-9), 190.4 (C-10) ppm; ν_{max}/cm^{-1} 3386, 2925, 1732, 1640, 1609, 1493, 1444, 1388, 1300, 1261, 1203, 1159, 1058, 1033, 1001, 959, 931, 831, 773, 735, 605, 478. HRMS (ESI, positive-ion): calc.: 337.0923 ($C_{16}H_{17}O_8$) [$(M + H)^+$] found: 337.0914. HPLC column: Chiralpak IA (250 mm 46 mm, Fa. Daicel); solvent: heptane/2-propanol = 70 : 30; flow rate: 0.5 mL min^{-1}, detection: 220 nm; t_R [(1*R*,2*S*,3*R*,4*S*)-**1**] 30.9 min; t_R [(1*S*,2*R*,3*S*,4*R*)-**1**] 44.1 min. RP-HPLC column: HyperClone (5 μm ODS (C18) 120 Å, LC Column 125 mm 4 mm, Fa. Phenomenex); solvent: H_2O : MeOH = 90 : 10 for 5 min, changed linearly to H_2O : MeOH = 40 : 60 (5–39 min) and to H_2O : MeOH = 0 : 100 (39–40 min), kept for 10 min (40–50 min) and changed linearly to H_2O : MeOH = 90 : 10 (50–51 min) and returned to the initial conditions within 19 min; flow rate: 5 ml min^{-1}; detection 220 nm; t_R = 26 min.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

We gratefully acknowledge the Ministry of Innovation, Science and Research of the German federal state of North-Rhine Westphalia, the Heinrich-Heine-Universität Düsseldorf, and the Forschungszentrum Jülich GmbH for their generous support of our projects. Furthermore, we thank the analytical departments and in particular Rudolf Hartmann and Kevin Bochinsky for their support of NMR measurements. Finally, we would like to thank Dr Dietrich Böse for his preliminary experiments and fruitful discussions.

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