DOI: 10.1002/ejoc.201301627

A Ring-Closing Enyne Metathesis Approach to Functionalized Semicyclic Dienes: The Total Synthesis of (–)-Tetrangomycin

Lindon W. K. Moodie[a] and David S. Larsen*[b]

Keywords: Total synthesis / Asymmetric synthesis / Natural products / Cycloaddition / Metathesis

The angucycline antibiotic (–)-tetrangomycin was synthesized in 13 steps (11 % overall yield) by using a stereoselective Diels–Alder reaction between a naphthoquinone and a semicyclic diene to construct the benz[*a*]anthraquinone ring system. The diene intermediates were synthesized through a ring-closing enyne metathesis reaction. The tertiary alcohol at C-3 was installed by an asymmetric dihydroxylation reaction. The relative stereochemistry of the dienes was verified by the NMR analyses of the cycloadducts that were obtained from their reaction with *N*-phenylmaleimide. Selective aromatization of the B ring was achieved under oxidative conditions.

Introduction

The angucycline antibiotics are one of the largest families of type II polyketide synthase natural products. Members typically contain a tetracyclic benz[*a*]anthracene scaffold, which characteristically differs by the degree of saturation, oxygenation, and glycosylation. Angucyclines display a range of biological activities, notably antibacterial and anticancer, which have spurred interest in their total synthesis, isolation, and biosynthesis. These aspects have been the subject of several comprehensive reviews,[1] the most recent of which was by Rohr and co-workers in 2012.[2] A commonly conserved substitution pattern among the angucyclines involves the oxygen functionality at the 1- and 3-positions as well as a methyl group at C-3 as exhibited by compounds **1**–**5** (see Figure 1).

We rationalized that access to a common synthetic intermediate that contains the 1,3-oxygenation and substitution pattern of the A ring could allow the syntheses of both naturally occurring angucyclines and their analogues. Of particular interested is (–)-tetrangomycin (**1**),[3] which has been identified as a potential drug lead against methicillin-resistant *Staphylococcus aureus* (MRSA).[4] Although various strategies have been employed for synthetic studies of the angucyclines,[5] the Diels–Alder reaction has proven to be a reliable and efficient approach to construct the benz[*a*]anthraquinone skeleton.[6] Furthermore, enantioenriched cycloadducts have been obtained by employing optically active dienophiles,[7] dienes,[6a,6d–6g,8] and chiral Lewis acids.[6c] The synthesis of (–)-tetrangomycin (**1**) by the Kaliappan research group employed a Diels–Alder approach in which C-3 functionalized diene **7**, synthesized by a ring-closing enyne metathesis (RCEM) reaction, was treated with bromojuglone **6** (see Scheme 1).[6a] Prior to isolation or characterization, the resulting cycloadduct was treated with base to effect the aromatization of the B ring and deacetylation. Removal of the protecting group and then photooxidation completed the total synthesis.

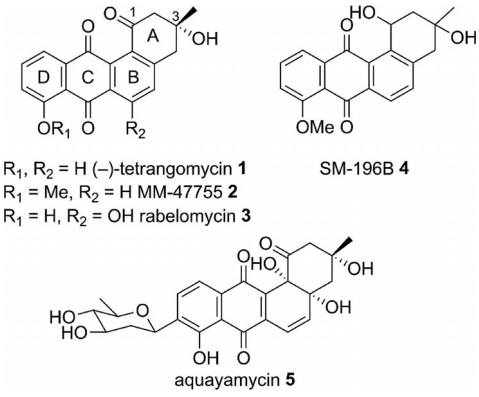
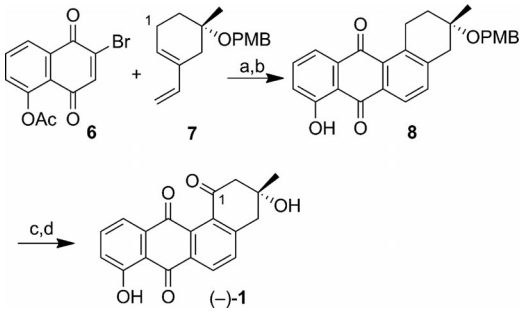


Figure 1. Examples of angucyclines that contain the C-3 methyl and hydroxy functionalities.

In the context of a general strategy towards a wider range of angucyclines, the use of diene **7** has its limitations. The introduction of the C-1 ketone functionality through a Norrish type II photooxidation is well established in angucycline chemistry.[6a,6c,7c,9] However, a general prerequisite for this transformation is the aromaticity of the B ring, which limits this approach to angucyclines that already contain this motif. Accessing angucyclines of greater complexity through further functionalization of the B ring would present significant synthetic challenges. Another drawback of

[a] Department of Chemistry, University of Tromsø, 9037 Tromsø, Norway
[b] Department of Chemistry, University of Otago, P. O. Box 56, Dunedin, New Zealand
E-mail: david.larsen@.otago.ac.nz
www.otago.ac.nz/chemistry

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/ejoc.201301627.



Scheme 1. Kaliappan synthesis of (–)-tetrangomycin (**1**).[6a] Reagents and conditions: (a) $C_6H_5CH_3$, 80 °C to 100 °C; (b) K_2CO_3, MeOH, 62% over two steps; (c) 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ), CH_2Cl_2, pH = 7 buffer, 0 °C, 93%; (d) *hv*, O_2, C_6H_6, 64% (PMB = *para*-methoxybenzyl).

dienes that lack substitution at C-1 is their lack of facial selectivity in Diels–Alder reactions.[6c] Concurrent research by our group is aimed at accessing enantiopure angucyclines that contain an oxygenated hydroaromatic functionality of the B ring (e.g., J-124131[10] aglycone **12**, see Figure 2). Synthetic studies of compounds that are structurally related to cycloadduct **11** have shown that the facial selectivity of the oxidation of the C-4a–C-5 alkene is dictated by the curved topology of the cycloadduct.[11] Hence, controlling the diastereoselectivity of the Diels–Alder reactions is of high priority.

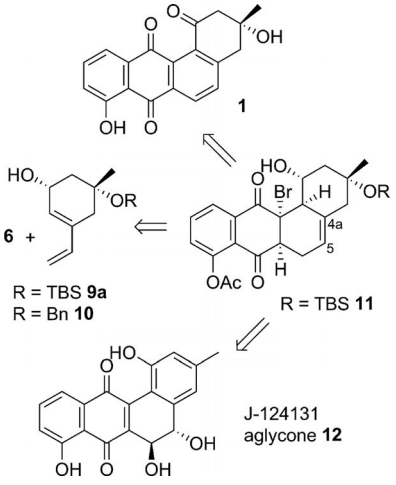


Figure 2. Functionalized diene **9a** as a proposed intermediate to angucyclines **1** and **12** (TBS = *tert*-butyldimethylsilyl).

Considering these limitations, we proposed the use of optically enriched diene **9a** (see Figure 2), which already contains the oxygen functionality at C-1 and, therefore, eliminates the need for a late-stage oxidation. Furthermore, it has been shown that semicyclic dienes that possess an allylic oxygen functionality at C-1 exhibit high levels of facial selectivity during Diels–Alder reactions with quinone-based dienophiles.[6d,6e,7b,11,12] However, a survey of the literature revealed a paucity of appropriately functionalized dienes. A rare example was reported by the Sulikowski group who synthesized **10** (see Figure 2) in an overall yield of 26% (14 steps) from a quinic acid derivative.[6d] A RCEM was identified as an attractive strategy to synthesize dienes of this type (see Figure 3).[13] Furthermore, Takayama and Fujishima reported the synthesis of appropriately functionalized enyne **13** during their studies of vitamin D analogues.[14] This report entails the synthesis of semicyclic dienes using a ring-closing enyne metathesis and demonstrates a proof of concept through the total synthesis of the angucycline (–)-tetrangomycin (**1**).

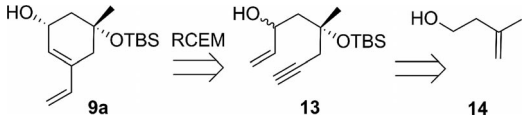
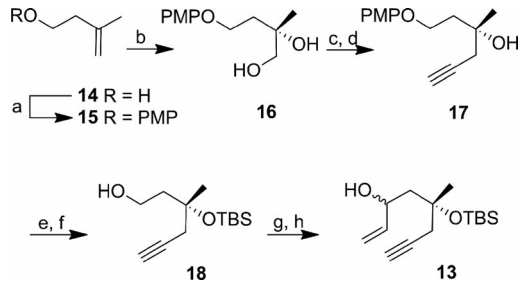


Figure 3. Retrosynthetic analysis of diene **9a**.

Results and Discussion

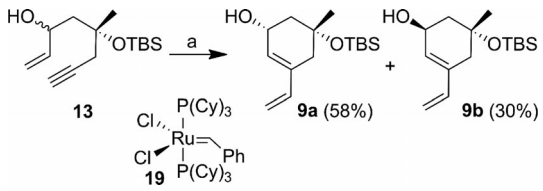
Using a strategy based on the work of Takayama and Fujishima,[14] the synthesis began with the protection of commercially available 3-methyl-but-3-en-1-ol (**14**) as its *para*-methoxyphenyl (PMP) ether **15** (see Scheme 2).



Scheme 2. The asymmetric synthesis of enyne **13**. Reagents and conditions: (a) *p*-$MeOC_6H_4OH$, Ph_3P, diisopropyl azodicarboxylate (DIAD), tetrahydrofuran (THF), 0 °C, 98%; (b) AD-mix-α, $CH_3SO_2NH_2$, *t*BuOH, H_2O, 0 °C, 99%; (c) *para*-toluenesulfonyl chloride (*p*TsCl), pyridine (py), 0 °C 95%; (d) lithium acetylide ethylenediamine, dimethyl sulfoxide (DMSO), 95%; (e) TBSOTf (OTf = trifluoromethylsulfonyl), collidine, CH_2Cl_2, quant.; (f) ceric ammonium nitrate (CAN), $MeCN/H_2O$, 0 °C, 87%; (g) Dess–Martin periodinane, CH_2Cl_2, 99%; (h) C_2H_3MgBr, $C_6H_5CH_3$, 95% (1.2:1.0 *dr*).

The Sharpless asymmetric dihydroxylation of **15** provided diol **16** in high yield (99%). The primary hydroxy group of **16** was tosylated followed by treatment with lithium acetylide ethylenediamine complex to afford **17** in 90% yield over two steps. The manipulation of the protecting groups afforded **18** in 87% yield from **17**. Following the oxidative deprotection of the PMP-protected alcohol, the sublimation of the benzoquinone byproduct prior to column chromatography aided in the purification of **18**. With alcohol **18** in hand, the sequence of oxidation and vinylation reactions could be initiated. The oxidation of **18** by treatment with Dess–Martin periodinane followed by treatment of the corresponding aldehyde with freshly prepared vinylmagnesium bromide yielded enyne **13** as an inseparable

mixture of diastereomers (approximately 1.2:1) in an overall yield of 72% from **14**. The success of our synthetic approach to tetrangomycin hinged upon the compatibility of the RCEM reaction with enyne **13** (see Scheme 3).

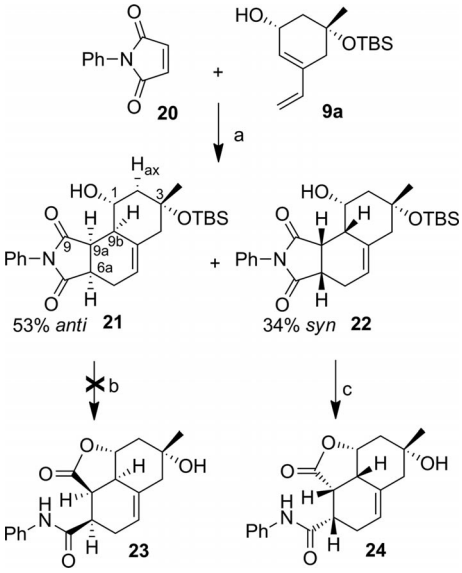


Scheme 3. The RCEM of enyne **13** to afford separable dienes **9a** and **9b**. Reagents and conditions: (a) **19** (10 mol-%), CH_2Cl_2 (0.045 M solution), argon, **9a** (58%), **9b** (30%).

The reaction conditions were screened to find that when the RCEM of **13** was conducted using Grubbs first generation catalyst (**19**, 10 mol-%) under argon, chromatographically separable dienes **9a** and **9b** (faster and slower eluting, respectively) were produced in a combined yield of 88%. Attempts to discern the relative stereochemistry at C-1 and C-3 of these dienes by using NOESY experiments were not conclusive, but **9a** and **9b** were later found to be *cis* and *trans*, respectively (vide infra), with regard to these groups. Interestingly, no improvement to reaction yield was observed when an ethylene atmosphere[15] or other metathesis catalyst was utilized. The reactivity of **13** under an inert atmosphere could be attributed to its allylic hydroxy group, which has been shown to improve RCEM reactions.[16] Mosher's ester analysis of both **9a** and **9b** indicated the enantiomeric ratios of both dienes were greater than 95:5, which verified high levels of asymmetric induction during the Sharpless asymmetric dihyroxylation (SAD) reaction. Experimental work establishing the synthetic route to tetrangomycin (**1**) was developed using the racemates of the compounds as described in Scheme 2 (see Supporting Information). Additionally, dienes (±)-**9a** and (±)-**9b** were used during the Mosher's ester analysis. Enyne (±)-**13** was synthesized in an overall yield of 66% from **14** using a synthetic sequence analogous to the asymmetric route, that is, aside from replacing the SAD reaction with an Upjohn dihydroxylation. The RCEM products, dienes (±)-**9a** and (±)-**9b**, were obtained in 47 and 36% yield, respectively, after column chromatography.

Although it was unknown how new dienes **9a** and **9b** would act in a Diels–Alder reaction, it warranted investigation. Their reaction with *N*-phenylmaleimide (**20**) might result in cycloadducts with sufficient rigidity to allow determination of the relative configurations. With this in mind, a solution of the faster eluting diene **9a** was treated with *N*-phenylmaleimide (**20**, see Scheme 4). The two cycloadducts **21** and **22** were separated by chromatography in 53 and 34% yield, respectively.

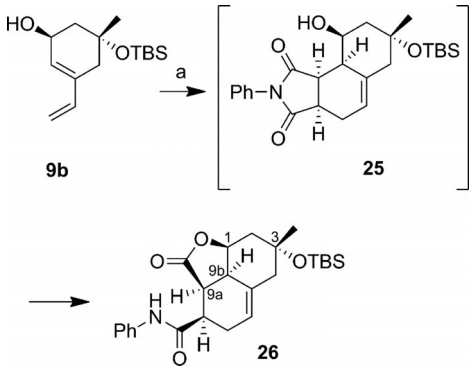
NOE correlations were instrumental in determining the relative orientations of the stereocenters at C-1, C-3, C-6a, C-9a, and C-9b of **21** and **22** (see Scheme 4). The hydrogen atoms at C-9a and C-9b of **21** were found to share a common face, which confirmed that **21** was formed through an *endo* transition state. Examination of vicinal coupling constants for the ^{1}H NMR spectroscopic data of **21** and a strong NOE correlation between H-2_{ax} and H-9b, suggested a pseudo-*trans*-diaxial relationship between H-1 and the H-9b and H-2_{ax} protons. This indicated that the cycloaddition to give **21** occurred through a transition state in which dienophile **20** approached **9a** from the face *anti* to the C-1 hydroxy group. Additionally, a strong NOE was observed between H-1 and the C-3 methyl group, which confirmed a *cis* relationship between the C-1 and C-3 oxygen functionalities of diene **9a**. A similar analysis of cycloadduct **22** revealed that it formed through an *endo-syn* transition state. To reinforce this conclusion, we reasoned that the C-1 hydroxy and C-9 imide carbonyl groups of *syn* adduct **22** were in sufficient proximity for lactonization, whereas in *anti* adduct **21**, these groups were on opposite faces and, thus, were unlikely to react. Our assumption was confirmed after **22** underwent lactonization (and concomitant TBS deprotection) under acidic conditions, but **21** remained unreacted. There appears to be no clear rationale for the differences in the facial selectivity exhibited by **9a** and **9b**. Therefore, further investigation and comparison of results to studies of the reactions of similar semicyclic dienes[17] are warranted.



Scheme 4. Diels–Alder reaction of diene **9a** with *N*-phenylmaleimide (**20**) and acid-catalyzed lactonization of **22** into **24**. Reagents and conditions: (a) C_6H_6, room temp., **21** (53%) and **22** (34%); (b) *para*-toluenesulfonic acid (*p*TSA), MeOH, room temp., no reaction; (c) *p*TSA, MeOH, room temp., 97%.

The Diels–Alder reaction between **20** and the slower eluting diene **9b** afforded an uncharacterized cycloadduct, according to the ^{1}H NMR analysis of the crude reaction material (see Scheme 5). Lactonization of this cycloadduct during chromatography afforded **26** as the sole product.

Strong NOE correlations between H-9b and both H-1 and H-9a along with the propensity for lactonization suggested that **26** stemmed from the *endo-syn* cycloadduct **25**, in which dienophile **20** approached **9b** from the same face



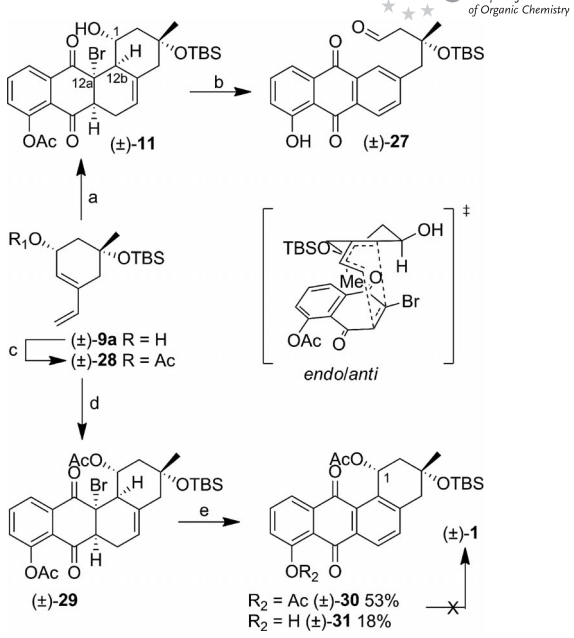
Scheme 5. Diels–Alder reaction of diene **9b** with *N*-phenylmaleimide (**20**) and subsequent lactonization to afford **26**. Reagents and conditions: (a) *N*-phenylmaleimide (**20**), C_6H_6, room temp., then SiO_2, 64%.

as the C-1 hydroxy group. NOESY studies of **26** were consistent with a *trans* relationship between the C-1 and C-3 oxygen functionalities of diene **9b**.

To explore the utility of these dienes with regard to the syntheses of angucyclines, (–)-tetrangomycin (**1**) was chosen as the target natural product because of its biological activities.[4] The evolution of drug resistance in *S. aureus* is a global health concern, and new classes of anti-infectious agents are required for its control.[18] A recent screening of approximately 1300 natural products that examined the inhibition of staphyloxanthin biosynthesis, a virulence factor produced by *S. aureus* that enhances host infection by scavenging reactive oxygen species,[19] revealed **1** as a promising drug lead.[4]

With diene (±)-**9a** in hand, the next synthetic transformation to examine was its Diels–Alder reaction with bromojuglone **6** (see Scheme 6). The reaction of the diene (±)-**9a** with **6** was conducted at 80 °C and afforded cycloadduct (±)-**11** as the sole diastereomer. The relative stereochemistry at C-12a, C-12b, and C-1 suggested that the product was formed through an *endo* transition state, in which the dienophile approached the face of the diene *anti* to the allylic hydroxy group (see Scheme 6). The aromatization of the B ring of cycloadduct (±)-**11** was attempted under basic conditions. Unfortunately, this resulted in fragmentation of the C-1–C-12b bond to form aldehyde (±)-**27**.

To avoid this undesired reactivity, diene (±)-**9** was acetylated under standard conditions. The Diels–Alder cycloaddition between (±)-**28** and **6** resulted in the isolation of (±)-**29** as a single diastereomer in 74% yield. The treatment of (±)-**29** with DBU afforded (±)-**30** and (±)-**31** in 53 and 14% yield, respectively. Although the NMR analysis of these compounds was indicative of B-ring aromatization, a full characterization proved difficult because of their instability. Additionally, (±)-**31**, with the C-8 phenolic functionality, was prone to epimerization at the C-1 stereocenter. Attempts to advance these compounds towards the synthesis of tetrangomycin (**1**) resulted in decomposition.

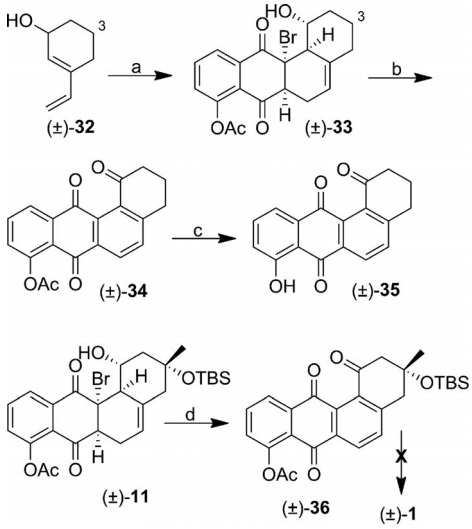


Scheme 6. First generation attempts towards tetrangomycin (**1**). Reagents and conditions: (a) **6**, $C_6H_5CH_3$, 80 °C, 66%; (b) 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU), C_6H_6, various temperatures (–15 °C, 0 °C, and r.t.), <65%; (c) Ac_2O, py, 4-(*N*,*N*-dimethylamino)pyridine (DMAP), CH_2Cl_2, 84%; (d) **6**, toluene, 100 °C, 74%; (e) DBU, CH_2Cl_2, (±)-**30** (53%), (±)-**31** (18%).

Following these unsuccessful approaches, we investigated an oxidative B-ring aromatization strategy[6d] of model cycloadduct (±)-**33**, which lacked the functionality C-3 [for the synthesis of (±)-**32**, see Supporting Information]. A screening of oxidants revealed that the treatment of (±)-**33** with pyridinium dichromate (PDC) followed by exposure to air effectively oxidized the C-1 hydroxy group to initiate the aromatization of the B ring. An unidentified byproduct of this reaction was often observed, and we believe this occurrence was associated with the required, long reaction times. The addition of 4 Å molecular sieves[20] allowed full conversion in 2 h and supressed the formation of a side product. The D-ring phenol of (±)-**35** was revealed by using lithium hydroxide.

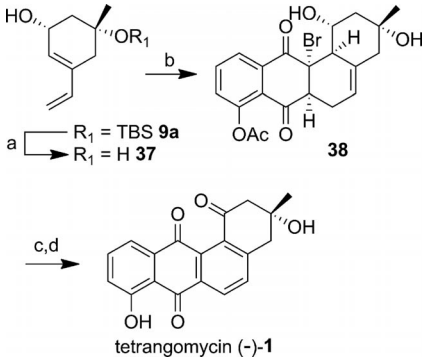
With this success, the PDC-mediated oxidative aromatization methodology was applied to cycloadduct (±)-**11** to afford (±)-**36** in 92% yield after chromatography (see Scheme 7). Unfortunately, all attempts to remove the TBS protecting group were met with decomposition. Investigations were conducted regarding the necessity of the TBS protecting group, and the optimum stage of the synthesis for its removal. However, the protection of the tertiary alcohol of enyne **13** was crucial for a successful RCEM reaction.[21]

After the RCEM, the treatment of diene **9a** with tetra-*n*-butylammonium fluoride (TBAF) afforded the requisite diol **37** (see Scheme 8). Interestingly, *trans*-oxygenated diene **9b** could not be deprotected under the screened reaction conditions. The Diels–Alder reaction between **6** and **37** yielded cycloadduct **38** in 87% yield. The oxidative aromatization followed by the deprotection of the phenol com-



Scheme 7. Oxidative B-ring aromatization of model compound (±)-**33** and its application towards tetrangomycin. Reagents and conditions: (a) **6**, $C_6H_5CH_3$, 70 °C, 88%; (b) PDC, molecular sieves (MS, 4 Å), CH_2Cl_2, 78%; (c) LiOH (0.1 M aqueous solution), THF, 0 °C, 71%; (d) PDC, MS (4 Å), CH_2Cl_2, then air, 92%.

pleted the total synthesis of (–)-tetrangomycin. The optical rotation and spectroscopic data of **1** were consistent with those previously reported.[5h,6c]



Scheme 8. Total synthesis of (–)-tetrangomycin (**1**). Reagents and conditions: (a) TBAF, 0 °C, THF, 77%; (b) **6**, $C_6H_5CH_3$, 80 °C, 87%; (c) PDC, MS (4 Å), CH_2Cl_2, 72%; (d) LiOH (0.1 M aqueous solution), THF, 0 °C, 54%.

Conclusions

We have described the synthesis of 1,3-functionalized semicyclic dienes **9a** and **9b**. The diene motif was forged by using a ring-closing enyne metathesis and Sharpless asymmetric dihydroxylation to form what becomes the C-3 stereocenter of the angucycline scaffold. Mosher's ester analysis of dienes **9a** and **9b** indicated that the SAD reaction formed diol **16** with an enantiomeric ratio of 95:5. To verify the potential of these dienes as synthetic intermediates for the angucycline natural products, (–)-tetrangomycin (**1**) was synthesized in an overall yield of 11% (13 steps) from commercially available alcohol **14**. The crucial transformations included a facially selective and regioselective Diels–Alder reaction with bromojuglone **6** and an oxidatively triggered B-ring aromatization. Further research by the Larsen group is focused on using these dienes to access angucyclines that contain B-ring oxygen functionality and their structural analogues.

Experimental Section

General Methods: The ^1H and ^{13}C NMR spectroscopic data were recorded either at 400 MHz with a Varian 400-MR NMR system or at 500 MHz with a Varian 500 MHz AR Premium Shielded spectrometer. Chemical shifts were referenced to the $CHCl_3$ residual solvent peak at δ = 7.26 ppm or the [D_5]acetone residual solvent peak at δ = 2.05 ppm. Chemical shifts of the carbon nuclei are reported relative to $CDCl_3$ at δ = 77.16 ppm and [D_6]acetone at δ = 29.84 ppm. High resolution mass spectrometry data were recorded with a Bruker microTOF mass spectrometer using electrospray ionization (ESI) in either the positive or negative modes. Infrared spectra were recorded with a Bruker Optics Alpha FTIR spectrometer [with a diamond attenuated total reflectance (ATR) top plate]. Optical rotations ($[\alpha]_D^T$) were recorded with a Jasco DIP-1000 digital polarimeter using a 100 mm cell. The rotations were measured using the sodium D line (589 nm) at ambient temperature. Samples were prepared at the reported concentration (g/100 mL) in the solvent indicated. Melting points were determined with a Mettler Toledo FP62 automatic melting point apparatus. Thin layer chromatography was performed with Merck aluminium-backed silica gel 60 (0.2 mm) plates. Compounds were initially detected by using ultraviolet light and iodine. TLC plates were developed using either a 5% w/v solution of dodecamolybdophosphoric acid in ethanol or an ethanolic vanillin stain with subsequent heating. Column chromatography was performed using silica gel (200–400 mesh, 40–63 μm). Anhydrous solvents were obtained from a PURE SOLV MD-6 solvent purification system. Powdered molecular sieves were flame-dried under vacuum immediately prior to use.

1-(4-Methoxyphenoxy)-3-methyl-3-butene (15):[14] DIAD (14.86 mL, 75.5 mmol) was added to a stirred solution of alcohol **14** (5.00 g, 58.1 mmol), *p*-methoxyphenol (21.60 g, 174.0 mmol), and triphenylphosphine (19.81 g, 75.5 mmol) in THF (125 mL) at 0 °C. The reaction mixture was then warmed to room temperature and stirred for 12 h. The solvent was removed under reduced pressure, and the resulting residue was dissolved in Et_2O (100 mL). Petroleum ether (300 mL) was added, and the mixture was stirred overnight to allow the precipitation of the triphenylphosphine oxide. After filtration and evaporation of solvent, the mixture was subjected to column chromatography (EtOAc/petroleum ether, 1:9) to give **15** (10.90 g, 98% yield) as a colorless oil. ^1H NMR (500 MHz, $CDCl_3$, 25 °C): δ = 6.86–6.82 (m, 4 H), 4.88–4.85 (m, 1 H), 4.83–4.81 (m, 1 H), 4.05 (t, $^3J_{H,H}$ = 6.9 Hz, 2 H), 3.78 (s, 3 H), 2.50 (t, $^3J_{H,H}$ = 6.9 Hz, 2 H), 1.83 (s, 3 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$, 25 °C): δ = 154.0, 153.2, 142.5, 115.7, 114.8, 112.1, 67.3, 55.8, 37.5, 23.0 ppm. IR (ATR): $\tilde{\nu}$ = 1505, 1225, 1038, 822, 735 cm^{-1}. HRMS (ESI): calcd. for $C_{12}H_{16}NaO_2$ $[M + Na]^+$ 215.1048; found 215.1023. $C_{12}H_{16}O_2$ (192.26): calcd. C 74.97, H 8.39; found C 75.10, H 8.68.

(+)-4-(4-Methoxyphenoxy)-2-methylbutane-1,2-diol [(+)-16]:[14] AD-mix-α (14.0 g) and methanesulfonamide (0.989 g, 10.4 mmol) were dissolved in a mixture of *tert*-butanol/H_2O (1:1, 70 mL), and the resulting mixture was cooled to 0 °C. To this, **15** (2.0 g, 10 mmol) was added dropwise, and the reaction was stirred for 14 h. After quenching with sodium sulfite (16.08 g), the mixture was stirred for

an additional 30 min. EtOAc (40 mL) was added, and the aqueous layer extracted with EtOAc (3× 40 mL). The combined organic extracts were washed with brine (20 mL) and dried with $MgSO_4$, and the solvent was removed under reduced pressure. The resulting residue was purified by column chromatography (EtOAc/petroleum ether, 4:1) to afford **16** (2.337 g, 99%) as a white solid; m.p. 52 °C. $[a]_D^{22}$ = +8.5 (*c* = 1.0, $CHCl_3$). ^1H NMR (500 MHz, $CDCl_3$, 25 °C): δ = 6.88–6.77 (m, 4 H), 4.21–4.06 (m, 2 H), 3.77 (s, 3 H), 3.50 (dd, $^3J_{H,H}$ = 11.1, 5.7 Hz, 1 H), 3.44 (dd, $^3J_{H,H}$ = 11.2, 5.9 Hz, 1 H), 2.10 (ddd, $^3J_{H,H}$ = 14.9, 7.9, 4.5 Hz, 1 H), 1.91 (ddd, $^3J_{H,H}$ = 14.9, 6.5, 4.3 Hz, 1 H), 1.25 (s, 3 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$, 25 °C): δ = 154.40, 152.44, 115.69, 114.88, 72.48, 70.22, 65.59, 55.87, 37.74, 24.32 ppm. IR (ATR): $\tilde{\nu}$ = 3314, 2918, 1506, 1465, 1222, 1165, 1048 cm^{-1}. HRMS (ESI): calcd. for $C_{12}H_{18}NaO_4$ [M + Na]$^+$ 249.1097; found 249.1091. $C_{12}H_{18}O_4$ (226.27): calcd. C 63.70, H 8.02; found C 63.33, H 8.00.

(–)-1-(4-Methoxyphenoxy)-3-methyl-5-hexyn-3-ol [(–)-17]

(+)-4-(4-Methoxyphenoxy)-2-methyl-1-(4-methylphenylsulfonyl)-2-butanol:[14] *p*TsCl (1.190 g, 6.2 mmol) was added to a solution of diol **16** (1.177 g, 5.2 mmol) in pyridine (10 mL) at 0 °C. The reaction was stirred for 3 h and then poured into H_2O (30 mL), and the product was extracted into Et_2O (3× 50 mL). The organic extracts were then washed with HCl (1 M aqueous solution, 20 mL), H_2O (20 mL), and brine (20 mL) and then dried with $MgSO_4$. After removal of the solvent, the crude residue was purified by column chromatography (EtOAc/petroleum ether, 1:1–3:1) to give the title compound (1.977 g, 95%) as a white solid; m.p. 51 °C. $[a]_D^{22}$ = +9.1 (*c* = 1.44, $CHCl_3$). ^1H NMR (500 MHz, $CDCl_3$, 25 °C): δ = 7.75 (d, $^3J_{H,H}$ = 8.2 Hz, 2 H), 7.28 (d, $^3J_{H,H}$ = 8.2 Hz, 2 H), 6.79–6.74 (m, 2 H), 6.74–6.70 (m, 2 H), 4.03–3.94 (m, 2 H), 3.91 (d, $^3J_{H,H}$ = 9.6 Hz, 1 H), 3.87 (d, $^3J_{H,H}$ = 9.6 Hz, 1 H), 3.72 (s, 3 H), 2.99 (s, 1 H), 2.38 (s, 3 H), 2.00–1.88 (m, 2 H), 1.22 (s, 3 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$, 25 °C): δ = 154.2, 152.4, 145.1, 132.6, 130.0, 128.0, 115.5, 114.7, 75.7, 71.0, 64.9, 55.8, 37.1, 24.5, 21.7 ppm. IR (ATR): $\tilde{\nu}$ = 3553, 2915, 1510, 1348, 1233, 1168, 1031, 963, 817, 671 cm^{-1}. HRMS (ESI): calcd. for $C_{19}H_{24}NaO_6S$ [M + Na]$^+$ 403.1186; found 403.1182. $C_{19}H_{24}O_6S$ (380.46): calcd. C 59.98, H 6.36, S 8.43; found C 59.97, H 6.28, S 8.23.

(–)-1-(4-Methoxyphenoxy)-3-methyl-5-hexyn-3-ol [(–)-17]:[14] Lithium acetylide–ethylenediamine complex (3.600 g, 39.0 mmol) was added to a solution of the prepared tosylate (2.464 g, 6.5 mmol) in DMSO (43 mL) under argon. The reaction was stirred for 16 h and then carefully quenched with H_2O (15 mL). The reaction mixture was then extracted into Et_2O (3× 30 mL), and the combined organic extracts were washed with brine (20 mL) and dried with $MgSO_4$. The solvent was removed in vacuo, and the resulting residue was purified by column chromatography (EtOAc/petroleum ether, 1:9–1:6) to provide **17** (1.490 g, 98%) as a colorless oil. $[a]_D^{22}$ = –14.9 (*c* = 1.0, $CHCl_3$). ^1H NMR (500 MHz, $CDCl_3$, 25 °C): δ = 6.88–6.78 (m, 4 H), 4.14–4.09 (m, 2 H), 3.73 (s, 3 H), 2.92 (s, 1 H), 2.45 (br. s, 2 H), 2.15–2.09 (m, 1 H), 2.08 (t, $^3J_{H,H}$ = 2.7 Hz, 1 H), 2.07–2.00 (m, 1 H), 1.36 (s, 3 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$, 25 °C): δ = 154.06, 152.54, 115.47, 114.69, 80.93, 71.53, 71.20, 65.49, 55.68, 39.13, 32.63, 26.79 ppm. IR (ATR): $\tilde{\nu}$ = 3452, 2932, 2116, 1506, 1467, 1224, 1031, 824, 735 cm^{-1}. HRMS (ESI): calcd. for $C_{14}H_{18}NaO_3$ [M + Na]$^+$ 257.1148; found 257.1150. $C_{14}H_{18}O_3$ (234.29): calcd. C 71.77, H 7.74; found C 71.77, H 7.93.

(–)-3-*tert*-Butyldimethylsilyloxy-3-methyl-5-hexyn-1-ol [(–)-18]

(–)-3-*tert*-Butyldimethylsilyloxy-1-(4-methoxyphenoxy)-3-methyl-5-hexyne:[14] *tert*-Butyldimethylsilyl triflate (2.88 mL, 12.3 mmol) was added dropwise to a solution of **17** (1.92 g, 8.2 mmol) and collidine (2.60 g, 25.0 mmol) in CH_2Cl_2 (10 mL) at 0 °C, and the reaction was stirred for 12 h. The mixture was then diluted with CH_2Cl_2 (50 mL), and the resulting solution was washed with H_2O (30 mL) and dried with $MgSO_4$. The solvent was then removed under reduced pressure, and the compound was purified by column chromatography (EtOAc/petroleum ether, 1:10) to afford the title compound (2.850 g, quant.) as a colorless oil. $[a]_D^{22}$ = –12.1 (*c* = 1.0, $CHCl_3$). ^1H NMR (500 MHz, $CDCl_3$, 25 °C): δ = 6.88–6.81 (m, 4 H), 4.13–4.08 (m, 2 H), 3.77 (s, 3 H), 2.47 (dd, $^3J_{H,H}$ = 16.5, 2.7 Hz, 1 H), 2.42 (dd, $^3J_{H,H}$ = 16.5, 2.7 Hz, 1 H), 2.17 (dt, $^3J_{H,H}$ = 14.0, 7.1, 7.1 Hz, 1 H), 2.04 (dt, $^3J_{H,H}$ = 14.0, 7.1, 7.1 Hz, 1 H), 2.03 (t, $^3J_{H,H}$ = 2.6 Hz, 1 H), 1.43 (s, 3 H), 0.90 (s, 9 H), 0.12 (s, 3 H), 0.11 (s, 3 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$, 25 °C): δ = 153.9, 153.3, 115.5, 114.8, 81.6, 74.4, 70.8, 64.9, 55.9, 41.0, 33.5, 28.0, 26.0, 18.4, –1.9, –2.0 ppm. IR (ATR): $\tilde{\nu}$ = 3309, 2119, 1617, 1441, 1227, 1039, 826, 772 cm^{-1}. HRMS (ESI): calcd. for $C_{20}H_{32}NaO_3Si$ [M + Na]$^+$ 371.2013; found 371.1999. $C_{20}H_{32}O_3Si$ (348.56): calcd. C 68.91, H 9.25; found C 69.81, H 9.31.

(–)-3-*tert*-Butyldimethylsilyloxy-3-methyl-5-hexyn-1-ol [(–)-18]:[14] A solution of the prepared silyl ether (0.546 g, 1.6 mmol) in acetonitrile (20 mL) and H_2O (6 mL) was stirred at 0 °C and then treated with ceric ammonium nitrate (2.04 g, 37.0 mmol). After 5 min, EtOAc (80 mL) and brine (80 mL) were added to the reaction mixture to partition it into organic and aqueous layers. The aqueous layer was separated and then extracted with EtOAc (3× 30 mL). The combined organic portions were washed with an aqueous solution of $NaHCO_3$ (10 mL), H_2O (10 mL), and brine (10 mL) and then dried with $MgSO_4$. The solvent was removed under reduced pressure, and the flask that contained the crude mixture was fitted with a reflux condenser and placed under vacuum. The flask was then warmed to 40 °C by using a water bath until a majority of the benzoquinone byproduct had sublimed to leave a brown oil. This residue was then purified by column chromatography (EtOAc/petroleum ether, 1:12–1:6) to provide **18** (0.331 g, 87%) as a brown oil. $[a]_D^{22}$ = –8.9 (*c* = 1.0, $CHCl_3$). ^1H NMR (500 MHz, $CDCl_3$, 25 °C): δ = 3.82–3.79 (m, 2 H), 2.48 (dd, $^3J_{H,H}$ = 16.5, 2.7 Hz, 1 H), 2.38 (dd, $^3J_{H,H}$ = 16.5, 2.7 Hz, 1 H), 1.99 (t, $^3J_{H,H}$ = 2.7 Hz, 1 H), 1.95 (dt, $^3J_{H,H}$ = 14.0, 6.0 Hz, 1 H), 1.81 (dt, $^3J_{H,H}$ = 14.0, 6.0 Hz, 1 H), 1.37 (s, 3 H), 0.85 (s, 9 H), 0.12 (s, 3 H) 0.11 (s, 3 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$, 25 °C): δ = 81.38, 76.38, 70.91, 59.75, 43.15, 32.94, 28.78, 25.99, 18.25, –1.78, –1.88 ppm. IR (ATR): $\tilde{\nu}$ = 3312, 2954, 2929, 2120, 1252, 1045, 1002, 832, 771, 626 cm^{-1}. HRMS (ESI): calcd. for $C_{13}H_{26}NaO_2Si$ [M + Na]$^+$ 265.1594; found 265.1569. $C_{13}H_{26}O_2Si$ (242.43): calcd. C 64.41, H 10.81; found C 65.15, H 10.61.

5-*tert*-Butyldimethylsilyloxy-5-methylocten-7-yn-3-ol (13)

(–)-3-*tert*-Butyldimethylsilyloxy-3-methyl-5-hexynal:[14] Alcohol **18** (248 mg, 1.0 mmol) in CH_2Cl_2 (3.0 mL) was added to a stirred solution of Dess–Martin periodinane (560 mg, 1.3 mmol) in CH_2Cl_2 (5 mL) under argon. The resulting mixture was stirred at room temperature for 8 h and then filtered through Celite. The filtrate was concentrated as the water bath temperature was kept below 20 °C, and the residue was purified by column chromatography (Et_2O/petroleum ether, 1:9) to afford the title compound (245 mg, 99%) as a colorless oil. The aldehyde was used immediately in the next reaction step. $[a]_D^{22}$ = –25.1 (*c* = 1.0, $CHCl_3$). ^1H NMR (500 MHz, $CDCl_3$, 25 °C): δ = 9.89 (t, $^3J_{H,H}$ = 2.8 Hz, 1 H), 2.72 (dd, $^3J_{H,H}$ = 15.0, 2.6 Hz, 1 H), 2.59–2.51 (m, 2 H), 2.45 (dd, $^3J_{H,H}$ = 16.6, 2.7 Hz, 1 H), 2.06 (t, $^3J_{H,H}$ = 2.7 Hz, 1 H), 1.45 (s, 3 H), 0.86 (s, 9 H), 0.13 (s, 3 H), 0.11 (s, 3 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$, 25 °C): δ = 202.65, 80.60, 74.30, 71.68, 54.59, 33.77, 28.10, 25.83, 18.27, –1.99 ppm.

5-*tert*-Butyldimethylsilyloxy-5-methylocten-7-yn-3-ol (13):[14] A solution of the aldehyde (418 mg, 1.7 mmol) in toluene (11.2 mL) was stirred under argon at –78 °C and then treated with freshly prepared vinylmagnesium bromide in THF (7.2 mL, 4.2 mmol). The reaction was warmed to room temperature and then stirred for 2 h. After quenching with saturated NH_4Cl (5 mL), the aqueous layer was extracted with EtOAc (3× 10 mL). The combined organic extracts were washed with brine (10 mL) and dried with $MgSO_4$. The solvent was removed in vacuo, and the compound was purified by column chromatography (Et_2O/petroleum ether, 1:9) to provide the title compounds (442 mg, 95%, inseparable mixture of diastereomers, 1.2:1) as a colorless oil. IR (ATR): $\tilde{\nu}$ = 3474, 3312, 2954, 2929, 2119, 1253, 1103, 990, 831, 772, 628 cm^{-1}. HRMS (ESI): calcd. for $C_{15}H_{28}NaO_2Si$ $[M + Na]^+$ 291.1751; found 291.1741. $C_{15}H_{28}O_2Si$ (268.47): calcd. C 67.11, H 10.51; found C 67.21, H 10.58. Data for diastereomer 1: ^1H NMR (500 MHz, $CDCl_3$, 25 °C): δ = 5.91–5.81 (m, 1 H), 5.28 (dt, $^3J_{H,H}$ = 17.1, 1.5 Hz, 1 H), 5.08 (ddt, $^3J_{H,H}$ = 10.4, 3.0, 1.5 Hz, 1 H), 4.52–4.44 (m, 1 H), 3.48 (t, $^3J_{H,H}$ = 1.7 Hz, 1 H), 2.53 (dd, $^3J_{H,H}$ = 16.4, 2.6 Hz, 1 H), 2.43 (dd, $^3J_{H,H}$ = 16.4, 2.7 Hz, 1 H), 2.04 (t, $^3J_{H,H}$ = 2.7 Hz, 1 H), 1.90 (dd, $^3J_{H,H}$ = 14.6, 10.1 Hz, 1 H), 1.76 (dd, $^3J_{H,H}$ = 14.6, 2.1 Hz, 1 H), 1.46 (s, 3 H), 0.89 (s, 9 H), 0.17 (s, 6 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$, 25 °C): δ = 141.22, 114.01, 81.13, 76.74, 71.29, 69.96, 47.41, 34.33, 26.73, 25.95, 18.21, –1.86 ppm. Data for diastereomer 2: ^1H NMR (500 MHz, $CDCl_3$, 25 °C): δ = 5.91–5.81 (m, 1 H), 5.28 (dt, $^3J_{H,H}$ = 17.1, 1.5 Hz, 1 H), 5.08 (ddt, $^3J_{H,H}$ = 10.4, 3.0, 1.5 Hz, 1 H), 4.52–4.44 (m, 1 H), 3.70 (t, $^3J_{H,H}$ = 1.7 Hz, 1 H), 2.66 (dd, $^3J_{H,H}$ = 16.5, 2.6 Hz, 1 H), 2.49 (ddd, $^3J_{H,H}$ = 16.5, 2.7, 1.1 Hz, 1 H), 2.02 (t, $^3J_{H,H}$ = 2.7 Hz, 1 H), 1.93 (dd, $^3J_{H,H}$ = 14.6, 2.2 Hz, 1 H), 1.69 (ddd, $^3J_{H,H}$ = 14.6, 10.4, 1.0 Hz, 1 H), 1.44 (s, 3 H), 0.88 (s, 9 H), 0.18 (s, 6 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$, 25 °C): δ = 141.14, 114.01, 80.99, 77.28, 71.27, 70.07, 47.11, 31.50, 28.90, 25.95, 18.13, –1.86 ppm.

3-*tert*-Butyldimethylsilyloxy-5-ethenyl-3-methylcyclohex-5-en-1-ol [(+)-9a and (+)-9b]: Grubbs first generation catalyst (35 mg 0.04 mmol) was added to a solution of enyne **13** (115 mg, 0.40 mmol) in CH_2Cl_2 (9.5 mL) under argon. After 24 h, the ^1H NMR spectrum of an aliquot from the reaction mixture revealed complete conversion. DMSO (150 µL, 2.1 mmol) was added, and the reaction mixture was stirred for an additional 16 h. The solvent was removed under reduced pressure, and the residue was subjected to column chromatography (EtOAc/petroleum ether, 1:15) to afford **9a** (56 mg, 58%) and the slower eluting diastereomer **9b** (35 mg, 30%). Data for **9a**: $[a]_D^{22}$ = +74.06 (c = 0.5, $CHCl_3$). ^1H NMR (500 MHz, $CDCl_3$, 25 °C): δ = 6.41 (dd, $^3J_{H,H}$ = 17.6, 10.8 Hz, 1 H), 5.91 (d, $^3J_{H,H}$ = 3.5 Hz, 1 H), 5.17 (d, $^3J_{H,H}$ = 17.6 Hz, 1 H), 5.05 (d, $^3J_{H,H}$ = 10.8 Hz, 1 H), 4.18 (br. s, 1 H), 3.34 (d, $^3J_{H,H}$ = 9.7 Hz, 1 H), 2.47 (d, $^3J_{H,H}$ = 18.1 Hz, 1 H), 2.10–2.05 (m, 1 H), 2.07–2.02 (m, 1 H), 1.73 (dd, $^3J_{H,H}$ = 13.9, 5.3 Hz, 1 H), 1.36 (s, 3 H), 0.83 (s, 9 H), 0.14 (s, 3 H), 0.04 (s, 3 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$, 25 °C): δ = 139.47, 134.27, 130.11, 112.76, 73.37, 65.74, 44.24, 38.01, 30.29, 25.88, 18.06, –1.96, –2.34 ppm. IR (ATR): $\tilde{\nu}$ = 3379, 2927, 2364, 1606, 1253, 1125, 1096 cm^{-1}. HRMS (ESI): calcd. for $C_{15}H_{28}NaO_2Si$ $[M + Na]^+$ 291.1751; found 291.1745. $C_{15}H_{28}O_2Si$ (268.47): calcd. C 67.11, H 10.51; found C 67.31, H 10.58. Data for **9b**: $[a]_D^{22}$ = +33.83 (c = 0.5, $CHCl_3$). ^1H NMR (500 MHz, $CDCl_3$, 25 °C): δ = 6.39 (dd, $^3J_{H,H}$ = 17.5, 10.8 Hz, 1 H), 5.76 (s, 1 H), 5.14 (d, $^3J_{H,H}$ = 17.6 Hz, 1 H), 5.02 (d, $^3J_{H,H}$ = 10.7 Hz, 1 H), 4.59–4.47 (m, 1 H), 2.30 (d, $^3J_{H,H}$ = 17.3 Hz, 1 H), 2.18 (dddd, $^3J_{H,H}$ = 12.3, 6.0, 2.1, 1.2 Hz, 1 H), 2.10 (dt, $^3J_{H,H}$ = 17.3, 2.5 Hz, 1 H), 1.38–1.32 (m, 1 H), 1.36 (s, 3 H), 0.79 (s, 9 H), 0.08 (s, 3 H), –0.01 (s, 3 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$, 25 °C): δ = 139.25, 135.09, 131.28, 112.54, 73.04, 67.22, 46.49, 38.31, 30.90, 25.84, 18.23, –2.04, –2.44 ppm. IR (ATR): $\tilde{\nu}$ = 3308, 2927, 2855, 2362, 1606, 1250, 1090, 1027, 990, 832, 805 cm^{-1}. HRMS (ESI): calcd. for $C_{15}H_{28}NaO_2Si$ $[M + Na]^+$ 291.1751; found 291.1725. $C_{15}H_{28}O_2Si$ (268.47): calcd. C 67.11, H 10.51; found C 67.39, H 10.68.

Cycloadducts (–)-22 and (–)-21: A solution of *N*-phenylmaleimide (9.2 mg, 0.053 mmol) and diene **9a** (15 mg, 0.056 mg) in toluene (250 µL) was stirred for 40 h under an inert atmosphere. The solvent was removed in vacuo. The resulting residue was purified by column chromatography (EtOAc/petroleum ether, 1:9–1:1) and then recrystallized (CH_2Cl_2 and petroleum ether) to yield **22** (8.5 mg, 34%) as a white solid; m.p. 147.1 °C. The column was then flushed with EtOAc, and the resulting eluent was removed under reduced pressure to yield **21** (13.2 mg, 53%) as an opaque gum. Data for **22**: $[a]_D^{22}$ = –129 (c = 0.22, $CHCl_3$). ^1H NMR (500 MHz, $CDCl_3$, 25 °C): δ = 7.45 (t, $^3J_{H,H}$ = 7.6 Hz, 1 H), 7.37–7.32 (m, 4 H), 5.75 (t, $^3J_{H,H}$ = 3.7 Hz, 1 H), 4.20 (dq, $^3J_{H,H}$ = 10.5, 2.9 Hz, 1 H), 3.75 (d, $^3J_{H,H}$ = 10.6 Hz, 1 H), 3.36 (t, $^3J_{H,H}$ = 9.5 Hz, 1 H), 3.19 (ddd, $^3J_{H,H}$ = 10.6, 9.5, 2.8 Hz, 1 H), 2.82 (d, $^3J_{H,H}$ = 19.1 Hz, 1 H), 2.64 (d, $^3J_{H,H}$ = 9.3 Hz, 1 H), 2.48 (ddq, $^3J_{H,H}$ = 19.2, 10.6, 3.3 Hz, 1 H), 2.42 (dd, $^3J_{H,H}$ = 13.0, 2.9 Hz, 1 H), 2.13 (d, $^3J_{H,H}$ = 13.1 Hz, 1 H), 2.00 (dt, $^3J_{H,H}$ = 14.6, 3.0 Hz, 1 H), 1.59 (dd, $^3J_{H,H}$ = 14.5, 3.1 Hz, 1 H), 1.32 (s, 3 H), 0.84 (s, 9 H), 0.16 (s, 3 H), 0.12 (s, 3 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$, 25 °C): δ = 178.91, 178.20, 132.72, 130.02, 129.17, 128.44, 127.09, 123.45, 77.47, 69.82, 50.34, 45.07, 40.98, 39.96, 36.54, 30.75, 26.11, 20.71, 18.19, –1.57, –1.61 ppm. IR (ATR): $\tilde{\nu}$ = 2955, 2929, 1702, 1383, 1252, 1193, 1145, 1093 cm^{-1}. HRMS (ESI): calcd. for $C_{25}H_{35}NNaO_4Si$ $[M + Na]^+$ 464.2228; found 464.2197. Data for **21**: $[a]_D^{22}$ = –48 (c = 0.5, $CHCl_3$). ^1H NMR (500 MHz, $CDCl_3$, 25 °C): δ = 7.46 (t, $^3J_{H,H}$ = 7.6 Hz, 2 H), 7.39 (t, $^3J_{H,H}$ = 7.4 Hz, 1 H), 7.21 (d, $^3J_{H,H}$ = 8.2 Hz, 2 H), 5.65 (s, 1 H), 4.22 (td, $^3J_{H,H}$ = 9.9, 5.6 Hz, 1 H), 3.65 (t, $^3J_{H,H}$ = 8.3 Hz, 1 H), 3.24 (ddd, $^3J_{H,H}$ = 8.5, 7.0, 4.3 Hz, 1 H), 2.62 (dt, $^3J_{H,H}$ = 16.0, 4.9 Hz, 1 H), 2.50 (t, $^3J_{H,H}$ = 8.9 Hz, 1 H), 2.32 (d, $^3J_{H,H}$ = 16.0 Hz, 1 H), 2.24 (d, $^3J_{H,H}$ = 14.4 Hz, 1 H), 2.21–2.13 (m, 2 H), 1.81 (dd, $^3J_{H,H}$ = 13.5, 10.1 Hz, 1 H), 1.26 (s, 3 H), 0.83 (s, 9 H), 0.10 (s, 3 H), 0.07 (s, 3 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$, 25 °C): δ = 178.77, 178.49, 137.47, 131.80, 129.33, 128.90, 126.60, 120.91, 73.20, 67.94, 48.00, 46.06, 43.43, 41.32, 40.03, 30.11, 25.87, 24.76, 18.07, –1.84, –1.95 ppm. IR (ATR): $\tilde{\nu}$ = 2924, 2853, 1699, 1499, 1378, 1252, 1183, 1139, 1037 cm^{-1}. HRMS (ESI): calcd. for $C_{25}H_{35}NNaO_4Si$ $[M + Na]^+$ 464.2228; found 464.2198.

Lactonization of (–)-22: *para*-Toluenesulfonic acid (approximately 1 mg) was added to a stirred solution of **22** (3.6 mg, 0.008 mmol) in MeOH (1.0 mL). After 4 h, TLC indicated the consumption of the starting material, and the solvent was removed under reduced pressure. The product was purified by column chromatography (EtOAc) to afford **24** (2.2 mg, 82%). ^1H NMR (500 MHz, $[D_6]$acetone, 25 °C): δ = 9.39 (s, 1 H), 7.65 (dd, $^3J_{H,H}$ = 8.7, 1.2 Hz, 2 H), 7.29 (dd, $^3J_{H,H}$ = 8.5, 7.5 Hz, 2 H), 7.04 (tt, $^3J_{H,H}$ = 7.6, 1.1 Hz, 1 H), 5.77 (dq, $^3J_{H,H}$ = 4.0, 2.0 Hz, 1 H), 4.83 (td, $^3J_{H,H}$ = 4.2, 1.9 Hz, 1 H), 3.78 (dd, $^3J_{H,H}$ = 6.0, 3.2 Hz, 1 H), 3.16 (s, 1 H), 2.93 (ddd, $^3J_{H,H}$ = 11.9, 6.1, 3.3 Hz, 1 H), 2.52 (dq, $^3J_{H,H}$ = 11.9, 2.6 Hz, 1 H), 2.49–2.41 (m, 1 H), 2.30–2.25 (m, 1 H), 2.20 (dt, $^3J_{H,H}$ = 15.8, 2.3 Hz, 1 H), 2.19 (dd, $^3J_{H,H}$ = 13.3, 2.5 Hz, 1 H), 1.91 (dd, $^3J_{H,H}$ = 16.2, 4.0 Hz, 1 H), 1.21 (s, 3 H) ppm. ^{13}C NMR (125 MHz, $[D_6]$acetone, 25 °C): δ = 177.33, 171.18, 140.40, 131.52, 129.44, 127.40, 124.12, 120.45, 80.63, 70.59, 47.01, 44.41, 42.35, 40.93, 39.34, 30.55, 25.38 ppm. HRMS (ESI): calcd. for $C_{19}H_{21}NNaO_4$ $[M + Na]^+$ 350.1363; found 350.1364.

Lactone (–)-26: *N*-Phenylmaleimide (9.2 mg, 0.053 mmol) and (+)-**9b** (14.2 mg, 0.053 mg) were dissolved in toluene (300 µL), and the

resulting mixture was stirred for 30 h under an inert atmosphere. The solvent was removed in vacuo, and the resulting residue was purified by column chromatography (EtOAc/petroleum ether, 1:6–1:1). Recrystallization (CH_2Cl_2 and petroleum ether) provided **26** (15.0 mg, 64%) as a white solid; m.p. 259 °C. $[a]_D^{22}$ = –3.3 (*c* = 0.285, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$, 25 °C): δ = 10.01 (s, 1 H), 7.59 (d, $^3J_{H,H}$ = 7.6 Hz, 2 H), 7.32 (dd, $^3J_{H,H}$ = 8.5, 7.4 Hz, 1 H), 7.10 (t, $^3J_{H,H}$ = 7.4 Hz, 1 H), 5.76 (dd, $^3J_{H,H}$ = 4.5, 1.8 Hz, 1 H), 4.78 (td, $^3J_{H,H}$ = 4.3, 2.3 Hz, 1 H), 3.45 (dd, $^3J_{H,H}$ = 6.0, 2.7 Hz, 1 H), 3.00 (s, 1 H), 2.93 (ddd, $^3J_{H,H}$ = 12.5, 5.6, 2.8 Hz, 1 H), 2.55 (dtt, $^3J_{H,H}$ = 17.1, 4.7, 2.0 Hz, 1 H), 2.46 (ddq, $^3J_{H,H}$ = 17.8, 12.5, 2.5 Hz, 1 H), 2.32–2.27 (m, 2 H), 2.23 (d, $^3J_{H,H}$ = 12.8 Hz, 1 H), 1.90 (dd, $^3J_{H,H}$ = 15.6, 4.3 Hz, 1 H), 1.20 (s, 3 H), 0.86 (s, 9 H), 0.11 (s, 3 H), 0.11 (s, 3 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$, 25 °C): δ = 178.33, 171.37, 138.49, 131.49, 129.06, 126.39, 124.27, 120.06, 80.41, 73.31, 48.74, 43.65, 43.27, 42.14, 41.78, 28.36, 26.27, 25.85, 18.06, –1.72, –1.75 ppm. IR (ATR): $\tilde{\nu}$ = 3316, 2927, 1756, 1693, 1597, 1530, 1438, 1239, 1182, 1144, 1112 cm^{-1}. HRMS (ESI): calcd. for $C_{25}H_{35}NNaO_4Si$ $[M + Na]^+$ 464.2228; found 464.2218.

(±)-8-Acetoxy-12a-bromo-3-*tert*-butyldimethylsilyloxy-1,2,3,4,6,6a,12a,12b-octahydro-1-hydroxy-3-methylbenz[*a*]anthracene-7,12-dione [(±)-11]: Bromojuglone **6** (19 mg, 0.065 mmol) was added to a solution of (±)-**9a** (17.5 mg, 0.065 mmol) in toluene (640 μL). The reaction mixture was heated at 80 °C for 12 h. Upon concentration of the reaction mixture, the residue was purified by flash column chromatography through a short plug of silica (EtOAc/petroleum ether, 1:4–1:1), and the product was triturated with CH_2Cl_2 and petroleum ether to afford (±)-**11** (24.4 mg, 66%) as a white amorphous foam; m.p. >80 °C (dec). ^{1}H NMR (500 MHz, $CDCl_3$, 25 °C): δ = 8.16 (dd, $^3J_{H,H}$ = 7.9, 1.1 Hz, 1 H), 7.74 (t, $^3J_{H,H}$ = 7.9 Hz, 1 H), 7.34 (dd, $^3J_{H,H}$ = 8.0, 1.2 Hz, 1 H), 5.62 (s, 1 H), 3.60 (dd, $^3J_{H,H}$ = 6.0, 3.4 Hz, 1 H), 3.40 (br. s, 1 H), 2.95 (d, $^3J_{H,H}$ = 10.1 Hz, 1 H), 2.88 (d, $^3J_{H,H}$ = 19.1 Hz, 1 H), 2.54 (ddd, $^3J_{H,H}$ = 18.3, 6.0, 2.8 Hz, 1 H), 2.37 (s, 3 H), 2.30–2.22 (m, 2 H), 1.91 (dd, $^3J_{H,H}$ = 11.6, 3.4 Hz, 1 H), 1.56 (t, $^3J_{H,H}$ = 11.3 Hz, 1 H), 1.08 (s, 3 H), 0.82 (s, 9 H), 0.06 (s, 3 H), 0.05 (s, 3 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$, 25 °C): δ = 192.09, 190.09, 169.62, 148.64, 136.16, 135.07, 131.46, 129.04, 126.69, 125.91, 121.16, 72.97, 69.98, 68.52, 58.63, 56.24, 50.78, 50.76, 27.08, 25.83, 24.27, 21.15, 18.01, –1.83 ppm. IR (ATR): $\tilde{\nu}$ = 3480, 1775, 1693, 1594, 1257, 1179, 1132, 1037, 831, 772, 726 cm^{-1}. HRMS (ESI): calcd. for $C_{27}H_{36}{}^{79}BrO_6Si$ $[M + H]^+$ 563.1459; found 563.1465. $C_{27}H_{35}BrO_6Si$ (563.56): calcd. C 57.54, H 6.26; found C 57.75, H 6.50.

(±)-4-(5′-Hydroxy-9′,10′-dihydro-9′,10′-dioxoanthracene-2′-yl)-3-*tert*-butyldimethylsilyloxy-3-methylbutanal [(±)-27]: A solution of (±)-**11** (42 mg, 0.076 mmol) in benzene (3.8 mL) was cooled to 0 °C and treated with 1,8-diazabicycloundec-7-ene (12 μL, 0.084 mmol). After 5 min, the reaction was quenched with an aqueous solution of NH_4Cl (4 mL), and the product was extracted into Et_2O (2× 10 mL). The combined extracts were washed with H_2O (5 mL) and brine (5 mL) and then dried with $MgSO_4$. The solvent was removed under reduced pressure, and the product was purified by column chromatography (Et_2O/petroleum ether, 1:6–1:3) to afford (±)-**27** (22 mg, 65%) as an orange gum. ^{1}H NMR (500 MHz, $CDCl_3$, 25 °C): δ = 12.64 (s, 1 H), 9.91 (t, $^3J_{H,H}$ = 2.7 Hz, 1 H), 8.24 (d, $^3J_{H,H}$ = 7.9 Hz, 1 H), 8.14 (d, $^3J_{H,H}$ = 1.7 Hz, 1 H), 7.84 (dd, $^3J_{H,H}$ = 7.5, 1.1 Hz, 1 H), 7.68 (dd, $^3J_{H,H}$ = 8.4, 7.5 Hz, 1 H), 7.68 (dd, $^3J_{H,H}$ = 7.9, 1.9 Hz, 1 H), 7.31 (dd, $^3J_{H,H}$ = 8.4, 1.1 Hz, 1 H), 3.11 (d, $^3J_{H,H}$ = 13.1 Hz, 1 H), 3.04 (d, $^3J_{H,H}$ = 13.1 Hz, 1 H), 2.58 (dd, $^3J_{H,H}$ = 15.0, 2.9 Hz, 1 H), 2.53 (dd, $^3J_{H,H}$ = 14.8, 2.8 Hz, 1 H), 1.40 (s, 3 H), 0.90 (s, 9 H), 0.13 (s, 3 H), 0.03 (s, 3 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$, 25 °C): δ = 202.00, 188.72, 182.60, 162.71, 145.24, 136.83, 136.82, 133.69, 133.37, 131.92, 129.65, 126.88, 124.52, 119.72, 116.34, 75.20, 55.42, 49.73, 28.16, 26.04, 18.39, –1.75 ppm. IR (ATR): $\tilde{\nu}$ = 2928, 1636, 1599, 1455, 1356, 1262, 830, 771 cm^{-1}. HRMS (ESI): calcd. for $C_{25}H_{29}O_5Si$ $[M – 2H + H]^+$ 437.1779; found 437.1778.

(±)-1-Acetoxy-3-*tert*-butyldimethylsilyloxy-5-ethenyl-3-methylcyclohex-5-ene [(±)-28]: Diene (±)-**9a** (98 mg, 0.37 mmol) and 4-(dimethylamino)pyridine (approximately 1 mg) were dissolved in a mixture of pyridine (1 mL) and acetic anhydride (1 mL), and the reaction was stirred for 14 h under nitrogen. The reaction mixture was diluted with CH_2Cl_2 (10 mL), and the resulting solution was washed with HCl (1 M aqueous solution, 5 mL), an aqueous solution of $NaHCO_3$ (5 mL), H_2O (5 mL), and brine (5 mL). The organic extract was dried with $MgSO_4$, and the solvent was removed under reduced pressure. The residue was purified by column chromatography (Et_2O/petroleum ether, 1:5) to afford (±)-**28** (95 mg, 84%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 6.36 (dd, $^3J_{H,H}$ = 17.5, 10.8 Hz, 1 H), 5.60 (s, 1 H), 5.40 (ddd, $^3J_{H,H}$ = 8.8, 6.6, 2.6 Hz, 1 H), 5.22 (d, $^3J_{H,H}$ = 17.5 Hz, 1 H), 5.08 (d, $^3J_{H,H}$ = 10.8 Hz, 1 H), 2.29 (br. s, 2 H), 2.07 (dd, $^3J_{H,H}$ = 12.2, 6.7 Hz, 1 H), 2.06 (s, 3 H), 1.78 (dd, $^3J_{H,H}$ = 12.3, 8.7 Hz, 1 H), 1.25 (s, 3 H), 0.86 (s, 9 H), 0.11 (s, 3 H), 0.10 (s, 3 H) ppm. ^{13}C NMR (101 Hz, $CDCl_3$, 25 °C): δ = 170.95, 138.57, 138.00, 125.52, 113.73, 72.25, 70.13, 42.64, 39.53, 27.87, 25.86, 21.49, 18.09, –1.81, –1.82 ppm. IR (ATR): $\tilde{\nu}$ = 2955, 2928, 1734, 1373, 1233, 1198, 1126, 1023, 832 cm^{-1}. HRMS (ESI): calcd. for $C_{17}H_{30}NaO_3Si$ $[M + Na]^+$ 333.1856; found 333.1840. $C_{17}H_{30}O_3Si$ (310.51): calcd. C 65.76, H 9.74; found C 66.00, H 9.74.

(±)-1,8-Diacetoxy-12a-bromo-3-*tert*-butyldimethylsilyloxy-1,2,3,4,6,6a,12a,12b-octahydro-3-methylbenz[*a*]anthracene-7,12-dione [(±)-29]: Bromojuglone **6** (45 mg, 0.15 mmol) was added to a solution of (±)-**28** (66 mg, 0.21 mmol) in toluene (2 mL) under argon. The reaction was heated at 100 °C for 45 h, cooled to room temperature, and then concentrated under reduced pressure. Purification by column chromatography (EtOAc/petroleum ether, 1:9–1:3) and recrystallization (CH_2Cl_2 and petroleum ether) afforded (±)-**29** (68 mg, 74%) as thin white crystals; m.p. 75.4 °C. ^{1}H NMR (500 MHz, $CDCl_3$, 25 °C): δ = 8.07 (d, $^3J_{H,H}$ = 7.8 Hz, 1 H), 7.73 (t, $^3J_{H,H}$ = 7.9 Hz, 1 H), 7.37 (dd, $^3J_{H,H}$ = 8.0, 1.2 Hz, 1 H), 5.65 (s, 1 H), 3.59 (t, $^3J_{H,H}$ = 5.6 Hz, 1 H), 3.17 (d, $^3J_{H,H}$ = 10.3 Hz, 1 H), 2.82–2.66 (m, 1 H), 2.56–2.47 (m, 1 H), 2.36 (s, 3 H), 2.31 (dd, $^3J_{H,H}$ = 13.0, 1.8 Hz, 1 H), 2.27 (d, $^3J_{H,H}$ = 13.6 Hz, 1 H), 2.11 (d, $^3J_{H,H}$ = 11.7 Hz, 1 H), 1.77 (s, 3 H), 1.49 (t, $^3J_{H,H}$ = 11.1 Hz, 1 H), 1.19 (s, 3 H), 0.82 (s, 9 H), 0.06 (s, 3 H), 0.05 (s, 3 H) ppm. The signal for H-1 was not observed. ^{13}C NMR (125 MHz, $CDCl_3$, 25 °C): δ = 192.31, 189.48, 169.21, 168.93, 149.51, 149.06, 135.00, 134.82, 129.95, 126.24, 122.02, 72.29, 70.62, 57.09, 53.07, 50.82, 46.64, 26.75, 25.81, 21.51, 21.16, 20.93, 18.01, –1.83, –1.87 ppm. The resonances associated with C-7a and C-12a could not be determined. IR (ATR): $\tilde{\nu}$ = 2953, 1774, 1753, 1704, 1363, 1225, 1183, 1022, 834, 774, 730 cm^{-1}. HRMS (ESI): calcd. for $C_{29}H_{37}{}^{79}BrNaO_7Si$ $[M + Na]^+$ 627.1390; found 627.1384. $C_{29}H_{37}BrO_7Si$ (605.60): calcd. C 57.52, H 6.16; found C 57.66, H 6.37.

Aromatization of (±)-29: 1,8-Diazabicycloundec-7-ene (11 μL, 0.073 mmol) was added to a stirred solution of (±)-**29** (22 mg, 0.036 mmol) in CH_2Cl_2 (3 mL) in an open vessel. After 15 min, the reaction was quenched with saturated aqueous NH_4Cl (2 mL), and the product was extracted into Et_2O (2× 10 mL). The combined extracts were washed with H_2O (5 mL) and brine (5 mL) and then dried with $MgSO_4$. The solvent was removed in vacuo, and the

residue was subjected to column chromatography (EtOAc/petroleum ether, 1:1) to afford a minor product that was tentatively assigned as (±)-**31** (3.2 mg, 18%) as a yellow film and the slower eluting major product (±)-**30** (10 mg, 53%) as a yellow film. The instability of (±)-**30** and (±)-**31** precluded their full characterization. Data for (±)-**30**: ^{1}H NMR (500 MHz, [D$_6$]acetone, 25 °C): δ = 8.19 (d, $^3J_{H,H}$ = 8.0 Hz, 1 H), 8.12 (dd, $^3J_{H,H}$ = 7.8, 1.2 Hz, 1 H), 7.93 (t, $^3J_{H,H}$ = 7.9 Hz, 1 H), 7.71 (d, $^3J_{H,H}$ = 8.1 Hz, 1 H), 7.55 (dd, $^3J_{H,H}$ = 8.0, 1.2 Hz, 1 H), 6.76 (dd, $^3J_{H,H}$ = 6.7, 4.4 Hz, 1 H), 3.22 (d, $^3J_{H,H}$ = 16.3 Hz, 1 H), 3.06 (d, $^3J_{H,H}$ = 16.4 Hz, 1 H), 2.41 (s, 3 H), 2.37 (ddd, $^3J_{H,H}$ = 14.3, 6.8, 1.1 Hz, 1 H), 2.20 (ddd, $^3J_{H,H}$ = 14.3, 4.4, 1.7 Hz, 1 H), 1.91 (s, 3 H), 1.42 (s, 3 H), 0.74 (s, 9 H), 0.13 (s, 3 H), 0.04 (s, 3 H) ppm. ^{13}C NMR (125 MHz, [D$_6$]acetone, 25 °C): δ = 185.52, 182.27, 170.33, 169.63, 150.70, 145.00, 137.89, 136.33, 136.21, 136.15, 135.54, 132.46, 130.23, 127.89, 126.00, 124.85, 71.02, 68.82, 46.06, 43.83, 29.12, 26.05, 21.15, 20.85, 18.50, –1.82, –1.92 ppm. Data for (±)-**31**: ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 12.42 (s, 1 H), 8.32 (d, $^3J_{H,H}$ = 8.0 Hz, 1 H), 7.73 (dd, $^3J_{H,H}$ = 7.6, 0.8 Hz, 1 H), 7.65 (t, $^3J_{H,H}$ = 7.9 Hz, 1 H), 7.53 (d, $^3J_{H,H}$ = 8.0 Hz, 1 H), 7.28 (dd, $^3J_{H,H}$ = 7.7, 0.7 Hz, 1 H), 6.83 (dd, $^3J_{H,H}$ = 6.7, 4.8 Hz, 1 H), 3.16 (d, $^3J_{H,H}$ = 17.1 Hz, 1 H), 2.91 (d, $^3J_{H,H}$ = 16.7 Hz, 1 H), 2.33 (ddd, $^3J_{H,H}$ = 14.2, 6.9, 1.0 Hz, 1 H), 2.22 (ddd, $^3J_{H,H}$ = 14.7, 5.0, 1.6 Hz, 1 H), 1.96 (s, 3 H), 1.37 (s, 3 H), 0.75 (s, 9 H), 0.10 (s, 3 H), 0.02 (s, 3 H) ppm. HRMS (ESI): calcd. for $C_{27}H_{32}NaO_6Si$ [M + Na]$^+$ 503.1860; found 503.1865.

(±)-8-Acetoxy-12a-bromo-1,2,3,4,6,6a,12a,12b-octahydro-1-hydroxybenz[*a*]anthracene-7,12-dione [(±)-33]: Bromojuglone **6** (300 mg, 1.0 mmol) was added to a solution of (±)-**32** (140 mg, 1.1 mmol) in toluene (2 mL), and the resulting mixture was heated at 70 °C for 20 h. After cooling to room temperature, the solvent was removed under reduced pressure, and the product was recrystallized (CH_2Cl_2, Et_2O, and petroleum ether) to provide (±)-**33** (418 mg, 88%) as a white solid; m.p. 155 °C. ^{1}H NMR (500 MHz, $CDCl_3$, 25 °C): δ = 8.18 (dd, $^3J_{H,H}$ = 7.9, 1.2 Hz, 1 H), 7.74 (t, $^3J_{H,H}$ = 7.9 Hz, 1 H), 7.34 (dd, $^3J_{H,H}$ = 8.0, 1.2 Hz, 1 H), 5.62 (td, $^3J_{H,H}$ = 4.2, 1.5 Hz, 1 H), 3.62 (dd, $^3J_{H,H}$ = 6.2, 2.8 Hz, 1 H), 3.34 (br. s, 1 H), 2.96 (d, $^3J_{H,H}$ = 10.5 Hz, 1 H), 2.92 (d, $^3J_{H,H}$ = 17.6 Hz, 1 H), 2.52 (dtd, $^3J_{H,H}$ = 17.8, 5.7, 2.5 Hz, 1 H), 2.38 (s, 3 H), 2.29–2.25 (m, 1 H), 1.98–1.86 (m, 2 H), 1.75–1.67 (m, 1 H), 1.33–1.23 (m, 2 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$, 25 °C): δ = 192.15, 190.34, 169.63, 148.60, 136.42, 134.98, 134.77, 128.92, 126.65, 126.17, 118.31, 71.90, 70.23, 59.44, 56.03, 37.20, 35.83, 24.96, 23.64, 21.18 ppm. IR (ATR): $\tilde{\nu}$ = 3457, 2934, 1772, 1690, 1186, 1059, 727 cm^{-1}. HRMS (ESI): calcd. for $C_{20}H_{19}{}^{79}BrNaO_5$ [M + Na]$^+$ 441.0308; found 441.0301. $C_{20}H_{19}BrO_5$ (419.27): calcd. C 57.29, H 4.57, Br 19.08; found C 57.39, H 4.48, Br 18.48.

8-Acetoxy-2,3,4-trihydrobenz[*a*]anthracene-1,7,12-trione (34):[22] Pyridinium dichromate (18 mg, 0.048 mmol) and molecular sieves (4 Å, 48 mg) were added to a solution of (±)-**33** (10 mg, 0.024 mmol) in CH_2Cl_2 (4 mL) under argon. After 1 h, the reaction vessel was exposed to air, and the reaction was diluted with CH_2Cl_2. The resulting mixture was stirred vigorously for an additional 1 h. Et_2O (10 mL) was added, and the reaction mixture was filtered through Celite®. The solvent was removed, and the residue was purified by column chromatography (EtOAc/petroleum ether, 2:1) to afford **34** (6.2 mg, 78%) as yellow crystals; m.p. 199.3 °C. ^{1}H NMR (500 MHz, $CDCl_3$, 25 °C): δ = 8.21 (d, $^3J_{H,H}$ = 8.1 Hz, 1 H), 8.11 (dd, $^3J_{H,H}$ = 7.8, 1.2 Hz, 1 H), 7.78 (t, $^3J_{H,H}$ = 7.9 Hz, 1 H), 7.54 (d, $^3J_{H,H}$ = 8.1 Hz, 1 H), 7.39 (dd, $^3J_{H,H}$ = 8.0, 1.2 Hz, 1 H), 2.93 (t, $^3J_{H,H}$ = 6.0 Hz, 2 H), 2.90 (t, $^3J_{H,H}$ = 7.0 Hz, 2 H), 2.48 (s, 3 H), 2.23 (qd, $^3J_{H,H}$ = 6.8, 5.6 Hz, 2 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$, 25 °C): δ = 198.94, 183.36, 181.10, 169.61, 151.02, 149.92, 137.10, 136.26, 135.26*, 134.36, 133.12, 129.42, 129.37, 125.82, 124.26, 39.28, 30.17, 22.90, 21.31 ppm. *Two coincidental carbon signals. IR (ATR): $\tilde{\nu}$ = 2937, 2358, 1766, 1668, 1590, 1276, 1183 cm^{-1}. HRMS (ESI): calcd. for $C_{20}H_{14}NaO_5$ [M + Na]$^+$ 357.0733; found 357.0707. $C_{20}H_{14}O_5$ (334.33): calcd. C 71.85, H 4.22; found C 71.98, H 4.12.

2,3,4-Trihydro-8-hydroxybenz[*a*]anthracene-1,7,12-trione (35):[23] LiOH (0.1 M solution, 1.2 mL, 0.12 mmol) was added to a solution of **34** (16.0 mg, 0.05 mmol) in THF (1 mL) at 0 °C. After 2 h, the reaction was quenched with an aqueous solution of NH_4Cl (2 mL) and then diluted with EtOAc. The aqueous layer was extracted into EtOAc (2 × 5 mL), and the combined organic extracts were washed with brine and dried with $MgSO_4$. The solvent was removed under reduced pressure, and the crude product was recrystallized (CH_2Cl_2 and petroleum ether) to afford **35** (10 mg, 71%) as orange crystals; m.p. 174.8 °C. ^{1}H NMR (500 MHz, $CDCl_3$, 25 °C): δ = 12.30 (s, 1 H), 8.30 (d, $^3J_{H,H}$ = 8.0 Hz, 1 H), 7.70 (dd, $^3J_{H,H}$ = 7.5, 1.5 Hz, 1 H), 7.68–7.64 (m, 1 H), 7.57 (d, $^3J_{H,H}$ = 8.0 Hz, 1 H), 7.28 (dd, $^3J_{H,H}$ = 8.0, 1.5 Hz, 1 H), 2.94 (t, $^3J_{H,H}$ = 5.9 Hz, 2 H), 2.92 (t, $^3J_{H,H}$ = 7.0 Hz, 2 H), 2.27–2.20 (m, 2 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$, 25 °C): δ = 199.27, 187.71, 187.73, 162.25, 151.62, 137.18*, 136.04, 135.18, 133.65, 132.98, 128.96, 123.85, 119.81, 115.61, 39.24, 30.20, 22.84 ppm. *Two coincidental carbon signals. IR (ATR): $\tilde{\nu}$ = 2923, 1704, 1667, 1634, 1588, 1450, 1361, 1277, 1261, 1217, 780, 718 cm^{-1}. HRMS (ESI): calcd. for $C_{18}H_{12}NaO_4$ [M + Na]$^+$ 315.0628; found 315.0639. $C_{18}H_{12}O_4$ (292.29): calcd. C 73.97, H 4.14; found C 73.82, H 4.31.

(±)-8-Acetoxy-3-*tert*-butyldimethylsilyloxy-2,3,4-trihydro-3-methylbenz[*a*]anthracene-1,7,12-trione [(±)-36]: Pyridinium dichromate (27 mg, 0.071 mmol) and molecular sieves (4 Å, 35 mg) were added to a solution of (±)-**11** (10 mg, 0.018 mmol) in CH_2Cl_2 (1.7 mL) under argon. After 2 h, the reaction vessel was exposed to air, and the reaction was diluted with CH_2Cl_2. The resulting mixture was stirred vigorously for an additional 2 h. Et_2O (15 mL) was added, and the reaction mixture was filtered through Celite®. The solvent was removed under reduced pressure, and the residue was purified by column chromatography (EtOAc/petroleum ether, 1:2) to afford (±)-**36** (7.8 mg, 92%) as an amorphous orange solid. ^{1}H NMR (500 MHz, $CDCl_3$, 25 °C): δ = 8.23 (d, $^3J_{H,H}$ = 8.0 Hz, 1 H), 8.09 (dd, $^3J_{H,H}$ = 7.7, 1.2 Hz, 1 H), 7.77 (t, $^3J_{H,H}$ = 7.9 Hz, 1 H), 7.49 (d, $^3J_{H,H}$ = 8.1 Hz, 1 H), 7.38 (dd, $^3J_{H,H}$ = 8.0, 1.2 Hz, 1 H), 3.13 (dd, $^3J_{H,H}$ = 16.5, 1.3 Hz, 1 H), 3.09 (d, $^3J_{H,H}$ = 16.4 Hz, 1 H), 3.03 (dd, $^3J_{H,H}$ = 15.2, 1.6 Hz, 1 H), 2.92 (d, $^3J_{H,H}$ = 15.2 Hz, 1 H), 2.48 (s, 3 H), 1.50 (s, 3 H), 0.61 (s, 9 H), 0.10 (s, 3 H), 0.01 (s, 3 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$, 25 °C): δ = 196.57, 183.43, 181.11, 169.66, 149.85, 147.76, 137.45, 135.42, 135.39, 135.25, 134.28, 133.76, 129.76, 129.20, 125.83, 124.22, 74.81, 54.62, 45.65, 29.84, 25.54, 21.31, 17.98, –2.13, –2.17 ppm. IR (ATR): $\tilde{\nu}$ = 2949, 2361, 1766, 1663, 1592, 1278, 1192, 1110, 827, 771 cm^{-1}. HRMS (ESI): calcd. for $C_{27}H_{30}NaO_6Si$ [M + Na]$^+$ 501.1704; found 501.1691. $C_{27}H_{30}O_6Si$ (478.62): calcd. C 67.76, H 6.32; found C 67.64, H 6.17.

(+)-5-Ethenyl-3-methylcyclohex-5-en-1,3-diol [(+)-37]: TBAF (1.0 M in THF, 0.79 mL, 0.79 mmol) was added to a stirred solution of **9a** (71 mg, 0.26 mmol) in THF (4 mL) at 0 °C. After stirring for 4 h, the reaction mixture was diluted with EtOAc (20 mL), and H_2O (10 mL) was added. The aqueous layer was extracted with EtOAc (2 × 10 mL). The combined organic layers were washed with brine (10 mL) and dried with $MgSO_4$, and the solvent was removed in vacuo. The product was purified by column chromatography (EtOAc/petroleum ether, 1:2–1:1) to afford **37** (31 mg, 77%) as a colorless oil. $[\alpha]_D^{22}$ = +136.1 (c = 0.75, $CHCl_3$). ^{1}H NMR (500 MHz,

$CDCl_3$, 25 °C): δ = 6.42 (dd, $^3J_{H,H}$ = 17.6, 10.8 Hz, 1 H), 5.92 (d, $^3J_{H,H}$ = 4.1 Hz, 1 H), 5.23 (d, $^3J_{H,H}$ = 17.5 Hz, 1 H), 5.08 (d, $^3J_{H,H}$ = 10.8 Hz, 1 H), 4.33 (t, $^3J_{H,H}$ = 4.8 Hz, 1 H), 3.05 (s, 1 H), 2.51 (s, 1 H), 2.40 (d, $^3J_{H,H}$ = 17.4 Hz, 1 H), 2.18 (d, $^3J_{H,H}$ = 17.4 Hz, 1 H), 2.03 (d, $^3J_{H,H}$ = 14.2 Hz, 1 H), 1.79 (dd, $^3J_{H,H}$ = 14.2, 4.9 Hz, 1 H), 1.36 (s, 3 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$, 25 °C): δ = 139.17, 135.45, 128.80, 113.62, 69.74, 65.65, 42.13, 38.64, 30.57 ppm. IR (ATR): $\tilde{\nu}$ = 3339, 2967, 2923, 1605, 1411, 1373, 1012, 899 cm^{-1}. HRMS (ESI): calcd. for $C_9H_{14}NaO_2$ $[M + Na]^+$ 177.0886; found 177.0883.

(+)-8-Acetoxy-12a-bromo-1,2,3,4,6,6a,12a,12b-octahydro-1,3-dihydroxy-3-methylbenz[*a*]anthracene-7,12-dione [(+)-38]: A solution of diene **37** (24 mg, 0.16 mmol) and **6** (43 mg, 0.14 mmol) in toluene (1.1 mL) was heated at 80 °C for 20 h under argon. The solvent was removed. The residue was purified by column chromatography (EtOAc/petroleum ether, 2:1–1:0) and recrystallized (CH_2Cl_2 and petroleum ether) to give **38** (55 mg, 87%) as a white solid; m.p. 87.9 °C. $[\alpha]_D^{22}$ = +62.4 (*c* = 0.16, $CHCl_3$). ^{1}H NMR (500 MHz, [D_6]-acetone, 25 °C): δ = 8.08 (dd, $^3J_{H,H}$ = 7.9, 1.2 Hz, 1 H), 7.82 (t, $^3J_{H,H}$ = 7.9 Hz, 1 H), 7.44 (dd, $^3J_{H,H}$ = 8.0, 1.2 Hz, 1 H), 5.64 (dq, $^3J_{H,H}$ = 5.5, 2.1 Hz, 1 H), 3.78 (d, $^3J_{H,H}$ = 5.9 Hz, 1 H), 3.74 (d, $^3J_{H,H}$ = 6.5 Hz, 1 H), 3.64 (s, 1 H), 3.07 (br. s, 1 H), 2.99 (dd, $^3J_{H,H}$ = 18.0, 5.6 Hz, 1 H), 2.88 (d, $^3J_{H,H}$ = 10.7 Hz, 1 H), 2.51 (ddq, $^3J_{H,H}$ = 18.0, 5.9, 2.7 Hz, 1 H), 2.29 (s, 3 H), 2.20 (dd, $^3J_{H,H}$ = 12.3, 2.5 Hz, 1 H), 2.14 (d, $^3J_{H,H}$ = 12.9 Hz, 1 H), 1.80 (ddd, $^3J_{H,H}$ = 12.4, 4.6, 2.5 Hz, 1 H), 1.54 (dd, $^3J_{H,H}$ = 12.0, 11.0 Hz, 1 H), 0.96 (s, 3 H) ppm. ^{13}C NMR (125 MHz, [D_6]acetone, 25 °C): δ = 192.17, 189.59, 169.51, 149.33, 137.79, 135.56, 132.05, 129.25, 127.29, 127.08, 121.62, 69.99, 68.49, 68.39, 60.26, 56.10, 51.44, 51.22, 26.48, 23.91, 20.98 ppm. IR (ATR): $\tilde{\nu}$ = 3470, 3400, 2980, 2897, 1745, 1714, 1696, 1596, 1366, 1313, 1262, 1208 cm^{-1}. HRMS (ESI): calcd. for $C_{21}H_{21}{}^{79}BrNaO_6$ $[M + Na]^+$ 471.0414; found 471.0418.

(–)-Tetrangomycin [(–)-1]

(–)-8-Acetoxy-3-*tert*-butyldimethylsilyloxy-3-methyl-2,3,4-trihydrobenz[*a*]anthracene-1,7,12-trione:[3b] Pyridinium dichromate (85 mg, 0.23 mmol) and molecular sieves (4 Å, 142 mg) were added to a solution of **38** (32 mg, 0.07 mmol) in CH_2Cl_2 (8 mL) under argon. After 2 h, the reaction vessel was exposed to air, and the reaction was diluted with CH_2Cl_2. The resulting mixture was stirred vigorously for an additional 2 h. Et_2O (35 mL) was added, and the resulting mixture was filtered through Celite®. The solvent was removed under reduced pressure, and the residue was purified by column chromatography (EtOAc/petroleum ether, 1:2–3:1) to afford the title compound (18.8 mg, 72%) as a yellow solid; m.p. 179.4 °C (EtOAc/petroleum ether). $[\alpha]_D^{22}$ = –24.7 (*c* = 0.45, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$, 25 °C): δ = 8.25 (d, $^3J_{H,H}$ = 8.1 Hz, 1 H), 8.10 (dd, $^3J_{H,H}$ = 7.7, 1.3 Hz, 1 H), 7.78 (t, $^3J_{H,H}$ = 7.9 Hz, 1 H), 7.54 (d, $^3J_{H,H}$ = 8.1 Hz, 1 H), 7.39 (dd, $^3J_{H,H}$ = 8.1, 1.3 Hz, 1 H), 3.18 (s, 2 H), 3.12 (d, $^3J_{H,H}$ = 14.8 Hz, 1 H), 3.00 (d, $^3J_{H,H}$ = 14.8 Hz, 1 H), 2.48 (s, 3 H), 1.51 (s, 3 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$, 25 °C): δ = 196.76, 183.47, 180.99, 169.58, 149.89, 147.09, 137.26, 135.47, 135.32, 134.98, 134.50, 133.99, 130.04, 129.35, 125.78, 124.22, 72.77, 54.05, 44.19, 30.24, 21.30 ppm. IR (ATR): $\tilde{\nu}$ = 2919, 1770, 1700, 1690, 1665, 1590, 1267, 1182 cm^{-1}. HRMS (ESI): calcd. for $C_{21}H_{16}NaO_6$ $[M + Na]^+$ 387.0839; found 387.0811.

(–)-Tetrangomycin [(–)-1]:[3b,5h,6c] LiOH (0.1 M solution, 740 μL, 0.74 mmol) was added to a solution of the prepared 8-acetoxy tetrangomycin (9.0 mg, 0.025 mmol) in THF (2 mL) at 0 °C. After 3 h, the reaction was quenched with an aqueous solution of NH_4Cl (5 mL), and the resulting mixture was partitioned by the addition of EtOAc (15 mL). The aqueous layer was extracted into EtOAc (3 × 10 mL), and the combined organic extracts were washed with brine and dried with $MgSO_4$. The solvent was removed under reduced pressure, and the crude product was recrystallized (CH_2Cl_2 and petroleum ether) to afford (–)-**1** (4.2 mg, 54%) as yellow crystals; m.p. 164.5 °C. $[\alpha]_D^{22}$ = –133.6 (*c* = 0.25, $CHCl_3$).[5h,6c] ^{1}H NMR (500 MHz, $CDCl_3$, 25 °C): δ = 12.26 (s, 1 H), 8.33 (d, $^3J_{H,H}$ = 8.0 Hz, 1 H), 7.69–7.65 (m, 2 H), 7.56 (d, $^3J_{H,H}$ = 8.1 Hz, 1 H), 7.28 (dd, $^3J_{H,H}$ = 7.0, 2.5 Hz, 1 H), 3.18 (s, 2 H), 3.13 (d, $^3J_{H,H}$ = 14.8 Hz, 1 H), 3.02 (d, $^3J_{H,H}$ = 14.9 Hz, 1 H), 1.53 (s, 3 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$, 25 °C): δ = 197.04, 187.58, 183.20, 162.21, 147.66, 137.24, 136.31, 135.89, 135.34, 133.90, 133.83, 129.57, 123.81, 119.77, 115.56, 72.75, 54.10, 44.26, 30.35 ppm. IR (ATR): $\tilde{\nu}$ = 3504, 3389, 2923, 1697, 1670, 1634, 1588, 1453, 1360, 1265, 1216, 1157, 1110, 1075, 823, 782, 771, 719 cm^{-1}. HRMS (ESI): calcd. for $C_{19}H_{15}O_5$ $[M + H]^+$ 323.0914; found 323.0914.

Supporting Information (see footnote on the first page of this article): Copies of ^{1}H and ^{13}C NMR of key compounds as well as experimental protocols for the syntheses of (±)-**9a**, (±)-**9b**, and the Mosher's esters.

Acknowledgments

The authors would like to thank the John Edmond Postgraduate Scholarship in Chemistry (to L. W. K. M.) and the University of Otago for the financial support.

[1] a) K. Krohn, J. Rohr, *Top. Curr. Chem.* **1997**, *188*, 127–195; b) J. Rohr, R. Thiericke, *Nat. Prod. Rep.* **1992**, *9*, 103–137; c) M. C. Carreno, A. Urbano, *Synlett* **2005**, 1–25.

[2] M. K. Kharel, P. Pahari, M. D. Shepherd, N. Tibrewal, S. E. Nybo, K. A. Shaaban, J. Rohr, *Nat. Prod. Rep.* **2012**, *29*, 264–325.

[3] a) M. Dann, D. V. Lefemine, F. Barbatschi, P. Shu, M. P. Kunstmann, L. A. Mitscher, N. Bohonos, *Antimicrob. Agents Chemother.* **1965**, *5*, 832–835; b) M. P. Kuntsman, L. A. Mitscher, *J. Org. Chem.* **1966**, *31*, 2920–2925.

[4] K. Sakai, N. Koyama, T. Fukuda, Y. Mori, H. Onaka, H. Tomoda, *Biol. Pharm. Bull.* **2012**, *35*, 48–53.

[5] a) K. Krohn, N. Böker, U. Flörke, C. Freund, *J. Org. Chem.* **1997**, *62*, 2350–2356; b) M. Yamaguchi, T. Okuma, A. Horiguchi, C. Ikeura, T. Minami, *J. Org. Chem.* **1992**, *57*, 1647–1649; c) K. Ohmori, K. Mori, Y. Ishikawa, H. Tsuruta, S. Kuwahara, N. Harada, K. Suzuki, *Angew. Chem.* **2004**, *116*, 3229; *Angew. Chem. Int. Ed.* **2004**, *43*, 3167–3171; d) K. Mori, K. Ohmori, K. Suzuki, *Angew. Chem.* **2009**, *121*, 5743; *Angew. Chem. Int. Ed.* **2009**, *48*, 5633–5637; e) X. Y. Yang, B. Q. Fu, B. Yu, *J. Am. Chem. Soc.* **2011**, *133*, 12433–12435; f) W. R. Roush, R. J. Neitz, *J. Org. Chem.* **2004**, *69*, 4906–4912; g) K. Sato, N. Asao, Y. Yamamoto, *J. Org. Chem.* **2005**, *70*, 8977–8981; h) C. Kesenheimer, A. Kalogerakis, A. Meissner, U. Groth, *Chem. Eur. J.* **2010**, *16*, 8805–8821.

[6] a) K. P. Kaliappan, V. Ravikumar, *J. Org. Chem.* **2007**, *72*, 6116–6126; b) K. Krohn, K. Khanbabaee, *Liebigs Ann. Chem.* **1994**, 1109–1112; c) J. S. Landells, D. S. Larsen, J. Simpson, *Tetrahedron Lett.* **2003**, *44*, 5193–5196; d) V. A. Boyd, G. A. Sulikowski, *J. Am. Chem. Soc.* **1995**, *117*, 8472–8473; e) K. Kim, V. A. Boyd, A. Sobti, G. A. Sulikowski, *Isr. J. Chem.* **1997**, *37*, 3–22; f) M. C. Carreño, M. Ribagorda, A. Somoza, A. Urbano, *Angew. Chem.* **2002**, *114*, 2879; *Angew. Chem. Int. Ed.* **2002**, *41*, 2755–2757; g) M. C. Carreno, A. Somoza, M. Ribagorda, A. Urbano, *Chem. Eur. J.* **2007**, *13*, 879–890.

[7] a) M. C. Carreno, A. Urbano, C. Di Vitta, *Chem. Commun.* **1999**, 817–818; b) M. C. Carreño, A. Urbano, J. Fischer, *Angew. Chem.* **1997**, *109*, 1695; *Angew. Chem. Int. Ed. Engl.* **1997**,

36, 1621–1623; c) M. C. Carreno, A. Urbano, C. Di Vitta, *Chem. Eur. J.* **2000**, *6*, 906–913.
[8] K. P. Kaliappan, V. Ravikumar, *Synlett* **2007**, 977–979.
[9] a) M. Oka, H. Kamei, Y. Hamagishi, K. Tomita, T. Miyaki, M. Konishi, T. Oki, *J. Antibiot.* **1990**, *43*, 967–976; b) K. Krohn, K. Khanbabaee, *Angew. Chem. Int. Ed. Engl.* **1994**, *33*, 99–100.
[10] S. Naito, K. Nakase, M. Tsukamoto, H. Nishioka, S. Nakajima, M. Hirayama, S. Yoshida (Banyu Pharmaceutical Co., Ltd., Japan), JP2001261688, **2001**.
[11] D. S. Larsen, M. D. O'Shea, *J. Org. Chem.* **1996**, *61*, 5681–5683.
[12] a) D. S. Larsen, M. D. O'Shea, *J. Chem. Soc. Perkin Trans. 1* **1995**, 1019–1028; b) M. C. Carreño, A. Urbano, C. Di Vitta, *J. Org. Chem.* **1998**, *63*, 8320–8330.
[13] S. T. Diver, A. J. Giessert, *Chem. Rev.* **2004**, *104*, 1317–1382.
[14] H. Takayama, T. Fujishima (Chugai Seiyaku Kabushiki Kaisha, Japan), EP1174424A1, WO2000064870, **2000**.
[15] M. Mori, N. Sakakibara, A. Kinoshita, *J. Org. Chem.* **1998**, *63*, 6082–6083.
[16] a) T. Imahori, H. Ojima, H. Tateyama, Y. Mihara, H. Takahata, *Tetrahedron Lett.* **2008**, *49*, 265–267; b) T. Imahori, H. Ojima, Y. Yoshimura, H. Takahata, *Chem. Eur. J.* **2008**, *14*, 10762–10771; c) Y. A. Lin, B. G. Davis, *Beilstein J. Org. Chem.* **2010**, *6*, 1219–1228.
[17] a) M. J. Fisher, W. J. Hehre, S. D. Kahn, L. E. Overman, *J. Am. Chem. Soc.* **1988**, *110*, 4625–4633; b) S. C. Datta, R. W. Franck, R. Tripathy, G. J. Quigley, L. Huang, S. Chen, A. Sihaed, *J. Am. Chem. Soc.* **1990**, *112*, 8472–8478; c) J. A. Funel, L. Ricard, J. Prunet, *Chem. Commun.* **2005**, 4833–4835.
[18] a) E. A. Bancroft, *JAMA, J. Am. Med. Assoc.* **2007**, *298*, 1803–1804; b) R. M. Klevens, M. A. Morrison, J. Nadle, S. Petit, K. Gershman, S. Ray, L. H. Harrison, R. Lynfield, G. Dumyati, J. M. Townes, A. S. Craig, E. R. Zell, G. E. Fosheim, L. K. McDougal, R. B. Carey, S. K. Fridkin, *JAMA, J. Am. Med. Assoc.* **2007**, *298*, 1763–1771.
[19] A. Clauditz, A. Resch, K. P. Wieland, A. Peschel, F. Gotz, *Infect. Immun.* **2006**, *74*, 4950–4953.
[20] S. Czernecki, C. Georgoulis, C. L. Stevens, K. Vijayakumaran, *Tetrahedron Lett.* **1985**, *26*, 1699–1702.
[21] a) C. S. Poulsen, R. Madsen, *J. Org. Chem.* **2002**, *67*, 4441–4449; b) J. A. Funel, J. Prunet, *J. Org. Chem.* **2004**, *69*, 5516–5516.
[22] V. A. Boyd, J. Reibenspies, G. A. Sulikowski, *Tetrahedron Lett.* **1995**, *36*, 4001–4004.
[23] J. R. Cui, Y. J. Jian, Y. K. Wu, S. M. Wang, *Chin. J. Chem.* **2006**, *24*, 1163–1169.

Received: October 30, 2013
Published Online: January 9, 2014

