The enantioselective total synthesis of nemotin[†]

Ya-Jun Jian and Yikang Wu*

Received 4th November 2009, Accepted 25th November 2009 First published as an Advance Article on the web 4th January 2010 DOI: 10.1039/b923123d

The allene-diyne natural product nemotin was synthesized for the first time through an enantioselective route with the stereogenic center at the lactone moiety derived from L-glutamic acid and the allene axis constructed from the corresponding propargylic tosylate, and the absolute configuration was thus established as (4S, 5aS).

Introduction

Nemotin (1) and the closely related nemotinic acid (2) were first isolated from fungi by Robbins¹ and co-workers in the 1940s. The preliminary biotesting showed that these two natural products possessed significant activity against a range of microorganisms. In 1955, Jones² and co-workers finished determination of the "planar" structure (Fig. 1) based on UV, IR, hydrogenation and elemental analysis data.



Fig. 1 The structure of nemotin, nemotic acid and phomallenic acids.

More detailed structural information, including the optical rotations of 1 and 2, were disclosed later in 1966.³ However, to the best of our knowledge, the relative as well as absolute configurations of these two compounds has never been assigned.

Recently, phomallenic acids (3) were identified⁴ as potent inhibitors for FabF, an essential enzyme in the bacterial type II fatty acid synthesis pathway (FAS II). As such a mode of action is entirely different from that of all previous antibacterial agents, the high antibacterial activity reported for phomallenic acids, nemotin and cepacin seems to imply that the allene-diyne unit shared by these compounds might be a pharmacophore for the antibacterial activity, making these types of molecules worthy targets for synthesis. Besides, as all the investigations on nemotin (1) were performed before NMR spectroscopy became a routine structural analysis tool, neither ¹H nor ¹³C NMR data of 1 and 2 are available to date. All these factors prompted us to carry out the work described below.

Results and discussion

Our strategy for the synthesis of 1 is depicted in Fig. 2. The allene axis was planned to be derived from the propargylic tosylate 6, either directly or via the bromoallene 5, through a coupling reaction with a proper diyne species. The configuration of the allene axis in either case is governed by that of the propargylic stereogenic center. Consequently, the relative configuration of the end product, nemotin 1, is decided by that of the hidden vicinal diol unit embedded in the propargylic tosylate.



Fig. 2 Outline of our retrosynthetic analysis of nemotin.

Because both the relative and absolute configuration of 1 was unknown at the outset, we arbitrarily chose one of the four possible isomers in the initial trial. The hidden diol motif carried in 7 can be derived from D-arabinose, an inexpensive and readily available chiral pool, and was therefore selected. The alkyne functionality was planned to be built up from the chloride 8 by treatment with LDA (lithium diisopropylamide) as similar⁵ transformations had been documented in the literature.

The synthetic endeavor was directed towards 8. As shown in Scheme 1, starting from D-arabinose via diol protection and chain

State Key Laboratory of Bioorganic and Natural Products Chemistry, Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, 345 Lingling Road, Shanghai, 200032, China. E-mail: yikangwu@mail.sioc.ac.cn [†] Electronic supplementary information (ESI) available: ¹H and ¹³C NMR spectra of all new compounds, and HPLC spectra of 48 and 51. See DOI: 10.1039/b923123d



Scheme 1 Reagents and conditions: (a) (i) $Me_2C(OMe)_2$, DMF, *p*-TsOH; (ii) $Ph_3P=CHCO_2Et$, toluene, $PhCO_2H$ (cat.), 90 °C, 62% from D-arabinose; (b) Pd–C, H₂, EtOAc, 89%; (c) NaH, BnBr, DMF, 53%, (d) LiAlH₄, THF, 89%; (e) PivCl, Et₃N, DMAP (cat.), 66%; (f) TBSOTF (1.5 eq.), 2,6-lutidine (2.0 eq.), 99%; (g) Pd(OH)₂, H₂ (1 atm), EtOH, 81%; (h) PPh₃, CCl₄, K₂CO₃, reflux, 69%.

extension, α , β -unsaturated ester **9** was obtained in 62% yield. The C–C double bond was subsequently saturated by hydrogenation over 10% Pd–C to deliver diol **10**. Further treatment with NaH and BnBr in DMF led to lactonisation of the secondary OH, while the primary one was masked as a benzyl ether.

The lactone was then reduced with LiAlH₄ to afford diol **12**, which was elaborated into **14** by selective protection of the primary OH as a Piv (pivaloyl) ester and TBS (*tert*-butyldimethylsilyl) protection of the secondary one. The Bn group was cleaved by hydrogenolysis over Pearlman's⁶ catalyst, providing alcohol **15**. Finally, replacement of the terminal OH group with a Cl by treatment with Ph₃P and CCl₄ gave desired **16** (which corresponds to **8** with R and R' being Piv and TBS, respectively) in 69% yield.

With chloride 16 in hand, we proceeded with the planned elimination. Unexpectedly, treatment of 16 with LDA did not lead to the corresponding alkyne 17, but the methyl ketone 18 (Fig. 3). Close inspection of the molecular structure suggested that because of the relative configuration of the hidden diol motif, the one on the chlorinated methylene group may be more hindered than those at the 1,3-dioxolane (Fig. 3).[‡] As a consequence, the LDA-mediated deprotonation occurred through pathway b rather than the usual one a, leading to the enol ether 20 instead of 19. Further hydrolysis of the acid-sensitive enol ether/acetonide during work-up gave the unexpected product 18.

Under the given circumstances, it seemed to us that using a smaller sized protecting group such as MOM (methoxymethyl) might increase the chance for the desired deprotonation to occur at the chlorinated methylene group. By then, all **16** had been consumed. To find a shorter route to **23**, the substrate needed for testing the elimination, instead of replacing the TBS group



Fig. 3 The possible cause for the formation of methyl ketone 18.

in 16 with a MOM, the synthesis took a bypass from alcohol 13 (Scheme 2). After masking the hydroxyl group as a MOM ether, the benzyl group was cleaved to free the terminal OH for transformation into a chloride. Unexpectedly, under the same conditions that were successful for converting 15 into 16 no discernible amount of chloride 23 was formed at all. The THF species 24 turned out to be the only isolable product. Conversion of 22 into 25 was possible (90%), but further transformation of the tosylate 25 into chloride 23 by treatment with LiCl and DMSO at rt again led to 24 (20%) as the only identifiable product in the complex product mixture.



Scheme 2 Reagents and conditions: (a) NaI (3.0 eq.), MOMCl (4.0 eq.), DIPEA (4.4 eq.), MeO(CH₂)₂OMe, 68%; (b) Pd(OH)₂ (20%), H₂, 100%; (c) PPh₃, CCl₄–CH₂Cl₂ (4:1), K₂CO₃, 78.6%.

The difficulties with the elimination and the length of the synthesis urged us to redirect our efforts to a more efficient approach, the one shown in Scheme 3. Thus, the known⁷ D-tartrate-derived acetonide **26** was reduced with DIBAL-H (diisobutylaluminium hydride) to give an intermediate dialdehyde, which upon further reaction with Ohira–Bestmann⁸ reagent, afforded diyne **27**. Introduction of only one ester group into **27** was troublesome. Use of commonly employed conditions⁹ (*n*-BuLi (1.5 eq.), $-78 \rightarrow -40$ °C, 1.5 h; then ClCO₂Et (1.3 eq.), -78 °C, 2 h, and then warmed to rt) led to **28** in only 30% yield, along with 21% of the undesired bis-ester. However, deprotonation with *n*-BuLi

[‡]One of the referees suggested that coordination of LDA may also contribute to this unexpected outcome.



Scheme 3 Reagents and conditions: (a) (i) DIBAL-H (2.0 eq.), toluene, $-78 \degree C, 2 h, (ii) CH_3COC(N_2)PO(OMe)_2 (3.0 eq.), K_2CO_3 (4.0 eq.), MeOH,$ 54% from 26; (b) (i) *n*-BuLi (1.0 eq.), THF, $-78 \rightarrow 0 \degree C, 2 h, (ii) ClCO_2Et$ (0.8 eq.), $-78 \degree C, 4 h, 49\%$ (along with 48% of recovered 27); (c) CuCl (0.5 eq.), NaBH₄ (4.0 eq.), MeOH, 60–90%; (d) (i) 50% aq. CF₃CO₂H, CH₂Cl₂, (ii) *p*-TsOH, CH₂Cl₂, 74% from 29; (e) *p*-TsCl, NEt₃, DMAP, CH₂Cl₂, 79%; (f) (i) TMSC=C-C=CTMS, MeLi-LiBr, THF, $-78 \degree C, 1.5 h$, then rt, 2 h, (ii) ZnBr₂, Pd(Ph₃P)₄, $-78 \rightarrow -20 \degree C, 3 h, 64\%$.

under more forcing conditions ($-78 \rightarrow 0$ °C, 2 h) and introduction of less ClCO₂Et (0.8 eq.) resulted in a substantially increased yield (49%), together with 48% of recovered recyclable starting **27**. We also tried the *t*-BuOK (1.0 eq.), DMSO, ClCO₂Et (0.8 eq.) conditions,¹⁰ but the product mixture was very complicated.

As we were not aware of any literature precedents of selective saturation of a conjugated C–C triple bond without affecting a co-existing isolated one, reduction of **28** to **29** was achieved under the CuCl/NaBH₄¹¹ conditions, which had been developed for similar reduction of conjugated C–C double bonds. The desired **29** was indeed formed; however, the yield fluctuated considerably and the over reduction product (with both triple bonds reduced) was very close to **29** on TLC, making the separation rather difficult. Mg/MeOH¹² conditions were also tested, but only the fully reduced product was observed.

Removal of the acetonide protecting group and formation of the lactone ring were then achieved by sequential treatment with 50% aq. CF_3CO_2H and *p*-TsOH in CH_2Cl_2 , resulting in the propargylic alcohol **30**, which, on further reaction with *p*-TsCl, yielded the corresponding tosylate **31**. The coupling with the diyne unit was carried out under conditions similar to those in Negishi¹³ couplings, affording the (4*R*,5a*R*)-allenediyne **32** in 64% yield. This compound, like nemotin, is rather unstable. On removal of the solvent, it deteriorated rapidly. Using usual techniques to acquire its spectroscopic data was therefore very difficult (*vide infra*).

To measure the diastereomeric ratio of **32**, we needed the other allene axial isomer (**37**) for comparison. One of the possible approaches would be conversion of **31** into bromoallene **33** (Scheme 4) because the coupling of bromoallenes with alkynes/diynes is known^{4c,14} to proceed with conversion of the allene axial configuration. However, the polarity of bromo-allene **33** and the concurrently formed **34** turned out to be very similar to each other, which made isolation of pure **33** unfeasible. Fortunately, Mitsunobu conversion of **30** led smoothly to **35**. These two diastereomers turned out to readily separable from each other on silica gel, ensuring us of the enantiopurity for each. Alcohol **35** was then tosylated to give **36**, which was further converted into **37** under the same conditions as employed for transformation of **31** to **32**. It is noteworthy that the (4*R*,5a*S*)



Scheme 4 Reagents and conditions: (a) CuBr, LiBr, THF, (b) (i) Ph₃P, DEAD, *p*-NO₂-benzoic acid, (ii) NaOH, H₂O, 76%; (c) *p*-TsCl, Et₃N, DMAP, CH₂Cl₂, 68%; (d) (i) TMSC=C-C=CTMS, MeLi-LiBr, THF, -78 °C, 1.5 h, then rt, 2 h, (ii) ZnBr₂, Pd(Ph₃P)₄, -78 \rightarrow -20 °C, 3 h, *cf.* the text.

isomer **37** is even more unstable than **32**; it deteriorated almost instantly on removal of the last drop of solvent. The sample of **37** for HPLC analyses thus had to be kept in solution all the time.

Another problem we encountered then was that **32** and **37** were inseparable by HPLC on several different types of columns, which made direct measurement of the d.e. values of these compounds impossible. Further derivatization of **32/37** was hence inevitable. However, the modified route (Schemes 3 and 4) leading to **32/37** was still rather lengthy. Accumulation of adequate amounts of the allenediynes for derivatization was still difficult—a better alternative had to be found. Then, we noticed a small detail that Jones^{1b} *et al.* had reported the specific rotation for the γ -lactone **38** (Fig. 4). Through literature searching, we also found the rotation data¹⁵ for such a lactone of an (*S*) configuration (**39**, Fig. 4). Judging from the sign of the specific rotations, the configuration of natural nemotin at C-4 should be opposite to that in **39** and those intermediates we synthesized above. The subsequent efforts were therefore directed to the lactone of the opposite configuration.



Fig. 4 Comparison of the two γ -lactones (38 and 39) reveals the C-4 configuration of 1 and 2. Note that saturation of the allene changes the substituent priority at the C-4: The (*S*)-isomer after saturation corresponds to the (*R*)-isomer in nemotin.

The new route (Scheme 5) started with the lactone-carboxylic acid **40**, which was readily derived from L-glutamic acid following the well-established literature¹⁶ procedure. Treatment with SOCl₂ at reflux for 3 h gave the crude acid chloride **41** in 99% yield.¹⁷



Scheme 5 Reagents and conditions: (a) $SOCl_2$, reflux, 3 h, 99% (crude); (b) HC=CMgCl, CuCl, -78 °C, 4 h, then -20 °C, 10 h, 31% for 42; *cf.* also the text and Table 1; (c) BH₃·SMe₂ (1.0 eq.), THF, -40 °C, (*R*)- or (*S*)-2-methyl-CBS-oxaza-borolidine (2 eq.), 92% (44/45 = 7:4) or 95% (44/45 = 4:17) with (*R*)- or (*S*)-2-methyl-CBS-oxaza-borolidine, respectively, or NaBH₄, CeCl₃, MeOH, 1 h, 34% (44/45 = 1.7:1).

Subsequent addition of an acetylene moiety to 41 was not as facile as expected in the beginning. Under the simplest conditions¹⁸ (TMSC=C-Li, -78 °C, 4 h), the product mixture was rather complex (Table 1, entry 1). Addition of a catalytic amount of CuCl¹⁹ to this system did not lead to any discernible improvements (entry 2). Use of TMSC≡CTMS and AlCl₃²⁰ to generate the corresponding aluminium species in situ also failed to afford the desired 42 (entry 3). The depressing situation then took a favaorable turn when attempts were made to use the corresponding magnesium reagents. With HC=CMgCl¹⁹ as the nucleophile, the desired 42 was obtained, though the yield was only 7% (entry 4). The introduction of 0.1 molar equivalents of CuCl increased the yield of 42 to 14% (entry 5). However, further reaction at higher temperatures did not lead to more 42. Instead, the undesired 43 became the only isolable product (entry 6). Therefore, in the end we decided to use only a small amount of CuCl and keep the reaction at temperatures below -20 °C.

The ketone **42** was reduced to corresponding alcohols **44** and **45**. Under Luche²¹ conditions (NaBH₄, CeCl₃, MeOH, 0 °C) the total yield was 45%, with a **44/45** (which were readily separable from each other on silica gel) ratio of 7:4. CBS²² (Corey–Bakshi–Shibata) reduction (BH₃, (*R*)- or (*S*)-2-methyl-CBS-oxaza-borolidine, 0 °C) gave better total yields (92% or 95% with the (*R*)- or (*S*)-oxazaborolidine catalyst, respectively).

The (S,S) propargyl alcohol **44** was then converted to the corresponding tosylate **46** under the conventional conditions

 Table 1
 Addition of various acetylene species to acid chloride 41

Entry	Conditions	Outcome
1	TMSC≡CLi, −78 °C, 4 h	Complex
2	TMSC≡CLi, CuCl (0.1 eq.), −78 °C, 4 h	Complex
3	TMSC≡CTMS, AlCl₃, rt	Complex
4	HC≡CMgCl, −78 °C, 4 h	42 (7%)
5	HC≡CMgCl, CuCl (0.1 eq.), −78 °C, 4 h	42 (14%)
6	HC≡CMgCl, CuCl (0.1 eq.), -78 °C, 4 h, then slowly to rt	43 (26%)
7	$HC \equiv CMgCl, CuCl (0.04 \text{ eq.}), -78 \text{ °C}, 4 \text{ h}, $ then -20 °C, 10 h	42 (31%)

(Scheme 6). The latter was treated with TMSC=C-C=C-Zn in the presence of Pd(PPh₃)₄ to give the (4*S*,5a*S*)-allenediyne 47. Similar to its diastereomers 32 and 37, 47 is also very unstable. However, because this isomer is of the same configuration as natural nemotin, and hence is more important than the other ones, extra efforts were made to estimate the yield of the coupling step (*cf.* the Experimental).



Scheme 6 Reagents and conditions: (a) p-TsCl, Et₃N, DMAP, CH₂Cl₂, 90%; (b) (i) TMSC=C-C=CTMS, MeLi·LiBr, THF, -78 °C, 1.5 h, then rt, 2 h, (ii) ZnBr₂, Pd(Ph₃P)₄, -78 \rightarrow -20 °C, 3 h, 64%; (c) (i) AgNO₃, MeOH, (ii) NaCN, sat. NH₄Cl, 71% from **47**; (d) (i) DIBAL-H (5.0 eq.), CH₂Cl₂, (ii) Ac₂O, py, DMAP, CH₂Cl₂, rt, 73% from **47**.

Because we had already encountered difficulty in the HPLC separation of 32/37 (*vide supra*), a pair of isomers similar to 47/50, no efforts were made on direct measurement of the d.e. value of 47 and/or 50. Instead, 47 was reduced with DIBAL-H (diisobutylaluminium hydride) and acylated with Ac₂O to afford diacetate 48. For comparison, the other diastereomer 51 was also prepared in a similar fashion from 50 (which was even more unstable than 47) as shown in Scheme 7. The d.e. values of 48 and 51 (and consequently 47 and 50) were then successfully determined on a CHFT-IRALPAK IC column to be 88.7% and 49.1%, respectively. Finally, the isomer (47) of the desired configuration was desilyated with AgNO₃²³ in MeOH to give the end product (4S, 5aS)-1.



Scheme 7 Reagents and conditions: (a) p-TsCl, Et₃N, DMAP, CH₂Cl₂, 90%; (b) (i) TMSC=C-C=CTMS, MeLi·LiBr, THF, -78 °C, 1.5 h, then rt, 2 h, (ii) ZnBr₂, Pd(Ph₃P)₄, $-78 \rightarrow -20$ °C, 3 h; (c) (i) DIBAL-H (5.0 eq.), CH₂Cl₂, (ii) Ac₂O, py, DMAP, CH₂Cl₂, rt, 15% from **49**.

As mentioned for the natural nemotin earlier by the previous investigators, the (4*S*,5*aS*)-1 we obtained is also very unstable. Near the end of rotary evaporation, an insoluble brown precipitate formed suddenly, and essentially (4*S*,5*aS*)-1 no longer could be detected by TLC in the remaining supernatant. To acquire the yield as well as optical rotation data, low-boiling point solvents (CH₂Cl₂–pentane) were utilized in the column chromatography, which could be removed gradually by repeated dilution with CH₂Cl₂ followed by partial concentration on a rotary evaporator until the signals for pentane could no longer be detected on ¹H NMR. The (4*S*,5*aS*)-1 in the solution was quantitized by ¹H NMR in CD₂Cl₂ with methyl 4-iodobenzoate as the internal reference. The optical rotation was then measured to be +356.10 (*c* 0.20, CH₂Cl₂), which is in excellent agreement with the value reported in the literature for the natural nemotin ([α]²⁰₂ +350 (*c* 0.20, CH₂Cl₂).

The specific rotation data also indicate that the natural nemotin must be a mixture of allene axial isomers similar to our synthetic (4S,5aS)-1, which was approximately a 16.7:1 mixture as estimated from the 88.7% d.e. value (determined on 48). As phomallenic acid C, another natural allendiyne, has also been shown^{4c} to be a mixture instead of a single enantiomer, perhaps co-existence of the allene axial isomers is a common phenomenon for natural allenediynes.

Conclusions

Nemotin, an allenediyne lactone isolated nearly 60 years ago, has been synthesized through an efficient route. The relative as well as absolute configuration of this natural product is thus established to be (4*S*,5*aS*). The ¹H and ¹³C NMR data for the given structure are also available for the first time. En route to the total synthesis of natural nemotin, some interesting results were also obtained, including the abnormal formation of methyl ketone **18** in the LDAmediated elimination of **16**, selective reduction of conjugated triple bond in the presence of an isolated one (reduction of **28** to **29**), and direct coupling of a diyne unit with an optically-active propargylic tosylate mediated by zinc salt to yield the allenediyne motif. The new observations with the allenediyne species also help to accumulate the essential knowledge about this unstable and so far underinvestigated structural motif.

Experimental

General

¹H and ¹³C NMR were recorded on either a Varian Mercury 300 or a Bruker Avance 300 or a Bruker Avance 500 NMR Spectrometer. FT-IR spectra were taken on an FT-IR 440 or a Perkin Elmer 983 or a Nicolet Avatar 360 Infrared Spectrometer. EI-MS and EI-HRMS data were recorded on a HP5989A and a Waters Micromass GCT instrument, respectively. ESI-MS were measured on a PE Mariner API-TOF or an Agilent Technologies LC/MSD SL or a Shimadzu LCMS-2010EV Mass Spectrometer. ESI-HRMS and MALDI-HRMS were collected on a Bruker APEXIII 7.0 Tesla FT-MS and an IonSpec 4.7 Tesla FTMS spectrometer, respectively. Optical rotations were recorded on a Perkin-Elmer Polarimeter 341or an Agilent Technologies P-1030 Polarimeter. Melting points were taken on a micro melting point apparatus equipped with a microscope and were uncorrected. Elemental analyses were performed on an Elementar VarioEL III instrument. Dry solvents were obtained as follows: THF, Et₂O, MeO(CH₂)₂OMe and toluene were refluxed and distilled over Na/PhCOPh under argon prior to use. CH₂Cl₂, DMF, Et₃N, pyridine, *i*-Pr₂NEt and *i*-Pr₂NH were distilled over CaH₂ prior to use. PE (chromatography solvent) stands for petroleum ether (b.p. 60–90 °C). Other chemicals were all commercially available and were used as received.

Ethyl (2E,4R,5S,6R)-4,7-dihydroxy-5,6-(isopropylidendioxy)hept-2-enoate (9). A solution of D-arabinose (8.000 g, 53.29 mmol), Me₂C(OMe)₂ (20 cm³), and *p*-TsOH (monohydrate, 120 mg, 0.63 mmol) in dry DMF (100 cm³) was stirred at ambient temperature for 4 h. Powdered Na₂CO₃ (74 mg, 0.63 mmol) was added in portions with stirring. The solids were filtered off. The filtrate was concentrated on a rotary evaporator. The residue was chromatographed on silica gel (20:1 CH₂Cl₂–MeOH) to give the known²⁴ intermediate acetonide-hemiacetal as a white solid (9.509 g, 50 mmol, 93.8%). A portion of this solid (2.982 g, 15.7 mmol) was dissolved in toluene (70 cm³) and treated with Ph₃P=CHCO₂Et (8.187 g, 23.5 mmol) and PhCO₂H (96 mg, 0.79 mmol) at 90 °C with stirring for 10 h. The solvent was removed on a rotary evaporator. The residue was chromatographed $(1:2 \text{ PE}: \text{Et}_2\text{O})$ on silica gel to afford ester 9 (2.534 g, 9.73 mmol, 62% from the intermediate hemiacetal or 58.2% from arabinose) as a colorless oil: $[\alpha]_{D}^{26}$ -8.90 (c 2.40, CHCl₃). FT-IR (film) v_{max}: 3456, 2985, 2937, 1717, 1659, 1460, 1371, 1307, 1270, 1217, 1040, 869 cm⁻¹; ¹H NMR (300 MHz, CDCl₃): δ 6.98 (dd, J = 4.6, 15.4 Hz, 1H), 6.16 (dd, J = 1.7, 16.0 Hz, 1 H), 4.52-4.45 (m, 1H), 4.30 (dt, J = 6.7, 5.0 Hz, 1H), 4.25-4.15 (m, 3H), 3.95-3.77 (m, 2H), 3.47 (d, J = 6.2 Hz, OH, 1H), 2.98 (t, J = 5.7 Hz, OH, 1H), 1.51 (s, 3H), 1.36 (s, 3H), 1.29 (t, J = 7.2 Hz, 3H); ¹³C NMR (75 MHz, CDCl₃): δ 166.3, 146.4, 122.2, 108.7, 78.4, 76.9, 68.8, 60.7, 60.5, 26.9, 24.7, 14.2; ESI-MS m/z: 283.0 ([M + Na]⁺); ESI-HRMS calcd for C₁₂H₂₀O₆Na ([M + Na]⁺): 283.11521; found 283.11392.

(4R,5S,6R)-4,7-dihydroxy-5,6-(isopropylidendioxy)-Ethyl heptanoate (10). A mixture of 9 (3.924 g, 15.1 mmol) and 10% Pd–C (400 mg) in EtOAc (75 cm³) was stirred under H_2 (1 atm) for 5 h. The catalyst was filtered off. The filtrate was concentrated on a rotary evaporator and the residue was chromatographed (1:2 PE: Et₂O) on silica gel to afford 10 (3.500 g, 13.35 mmol, 89.1%) as a colorless oil: $[\alpha]_{D}^{23}$ +18.68 (c 1.70, CHCl₃). FT-IR (film) v_{max} : 3450, 2985, 2936, 1732, 1456, 1381, 1034 cm⁻¹; ¹H NMR (300 MHz, CDCl₃): δ 4.32 (dt, J = 6.9, 5.3 Hz, 1 H), 4.11 (q, J = 7.1 Hz, 2H), 4.02 (dd, J = 3.6, 6.8 Hz, 1H), 3.86-3.66 (m,3 H), 3.10 (t, J = 6.2 Hz, 1 H, OH), 2.99 (d, J = 6.2 Hz, 1H, OH), 2.50 (t, J = 7.2 Hz, 2H), 1.84 (q, J = 7.0 Hz, 2H), 1.47 (s, 3H), 1.34 (s, 3H), 1.23 (t, J = 7.1 Hz, 3H); ¹³C NMR (75 MHz, CDCl₃): *δ* 173.9, 108.2, 79.4, 77.2, 68.0, 60.8, 60.5, 30.2, 29.6, 27.1, 24.9, 14.1; ESI-MS m/z 285.1 ([M + Na]⁺); ESI-HRMS calcd for $C_{12}H_{22}O_6Na$ ([M + Na]⁺): 285.13086; found 285.1317.

(4*R*,5*S*,6*R*)-4-Hydroxy-5,6-(isopropylidendioxy)-7-benzyloxyheptanoic acid-1,4-lactone (11). A solution of 10 (279 mg, 1.07 mmol) in dry DMF (3 cm³) was added to a suspension of NaH (60% in mineral oil, 128 mg, 3.21 mmol) and BnBr (1.830 g, 1.3 mL, 10.70 mmol) in dry DMF (2 cm³) stirred at -40 °C. After completion of the addition, the bath temperature was allowed to warm naturally to ambient temperature. The mixture was stirred at the same temperature for 4 h before being diluted with EtOAc, washed with aq. sat. NH₄Cl, water, and brine, and dried over anhydrous Na₂SO₄. Removal of the solvent by rotary evaporation and column chromatography (1 : 1 PE : Et₂O) on silica gel afforded **11** (172 mg, 0.56 mmol, 53%) as a colorless oil: $[\alpha]_{D}^{24}$ -91.23 (*c* 1.10, CHCl₃). FT-IR (film) v_{max} : 3030, 2984, 2924, 1775, 1455, 1381, 1261, 1215, 1171, 1085, 739, 699 cm⁻¹; ¹H NMR (300 MHz, CDCl₃): δ 7.42-7.24 (m, 5H), 4.69-4.38 (m, 4H), 4.15 (d, *J* = 7.0 Hz, 1H), 3.77 (d, *J* = 6.5 Hz, 2H), 2.71-2.55 (m, 1H), 2.49-2.09 (m, 3H), 1.44 (s, 3H), 1.36 (s, 3H); ¹³C NMR (75 MHz, CDCl₃): δ 177.5, 137.6, 128.4, 127.89, 127.85, 109.3, 79.0, 77.1, 75.2, 73.6, 68.7, 27.9, 26.5, 25.0, 24.9; ESI-MS *m/z* 329.1 ([M + Na]⁺); ESI-HRMS calcd for C₁₇H₂₂O₅Na ([M + Na]⁺): 329.13594; found 329.13595.

(4R,5S,6R)-4-Hydroxy-5,6-(isopropylidendioxy)-7-bezyloxyheptanol (12). LiAlH₄ (285 mg, 7.5 mmol) was added to a solution of 11 (1.173 g, 3.83 mmol) in dry THF (15 cm³) stirred at 0 °C. The mixture was stirred at ambient temperature over night. Na₂SO₄·10H₂O was added. The mixture was stirred for 2 h. Solids were filtered off. The filtrate was washed with water and brine before being dried over anhydrous Na₂SO₄. Removal of the solvent by rotary evaporation and column chromatography (2:3 PE: Et₂O) on silica gel gave 12 (1.058 g, 3.41 mmol, 89%) as a colorless oil: $[\alpha]_{D}^{23}$ –2.36 (*c* 0.92, CHCl₃). FT-IR (film) v_{max} : 3431, 2984, 2926, 2869, 1454, 1380, 1246, 1217, 1166, 1089, 1028, 737, 699 cm⁻¹; ¹H NMR (300 MHz, CDCl₃): δ 7.40-7.28 (m, 5H), 4.57 (s, 2H), 4.33 (dd, J = 5.6, 11.7 Hz, 1H), 4.03 (dd, J = 4.1, 6.3 Hz, 1H), 3.76-3.60 (m, 5H), 2.89 (broad, OH, 1H), 2.31 (broad, OH, 1H), 1.76-1.52 (m, 4H), 1.49 (s, 3H), 1.37 (s, 3H); ¹³C NMR (75 MHz, CDCl₃): δ 137.4, 128.4, 127.94, 127.87, 108.3, 79.7, 75.8, 73.6, 69.2, 68.5, 62.6, 31.5, 29.4, 27.2, 25.0; ESI-MS m/z $333.2([M + Na]^+)$; ESI-HRMS calcd for C₁₇H₂₆O₅Na ([M + Na]^+): 333.16725; found 333.16704.

(4R,5S,6R)-4-Hydroxy-5,6-(isopropylidendioxy)-7-bezyloxyheptanyl 2,2-dimethylpropionate (13). To a solution of 12 (1.010 g, 3.26 mmol) in dry CH_2Cl_2 (15 cm³) stirred at 0 °C were added in turn Et₃N (1.36 cm³, 9.78 mmol), PivCl (0.52 cm³, 4.24 mmol), and DMAP (40 mg, 0.33 mmol). The mixture was stirred at ambient temperature overnight before being diluted with EtOAc, washed with aq. sat. NH₄Cl, water, and brine, and dried over anhydrous Na₂SO₄. Removal of the solvent by rotary evaporation and column chromatography $(2:1 \text{ PE}: \text{Et}_2 \text{O})$ on silica gel gave 13 (847 mg, 2.15 mmol, 66%) as a colorless oil: $[\alpha]_{D}^{23}$ -2.24 (c 0.60, CHCl₃). FT-IR (film) v_{max}: 3505, 2959, 2932, 2872, 1727, 1480, 1285, 1160, 1092, 737, 698 cm⁻¹; ¹H NMR (300 MHz, CDCl₃): δ 7.40-7.28 (m, 5 H), 4.60 (d, J = 12.4 Hz, 1H), 4.56 (d, J = 12.8 Hz, 1H), 4.35 (dd, J = 5.6, 12.1 Hz, 1H), 4.10-3.98 (m, 3H), 3.77-3.58 (m, 3H), 2.51 (d, J = 6.7 Hz, OH, 1H), 1.94-1.77 (m, 1H), 1.73-1.52 (m, 3H), 1.50 (s, 3H), 1.37 (s, 3H), 1.19 (s, 9H); ¹³C NMR (75 MHz, CDCl₃): δ 178.6, 137.5, 128.5, 127.94, 127.89, 108.3, 79.3, 75.9, 73.7, 68.8, 68.6, 64.2, 38.7, 31.2, 27.2, 27.1, 25.1, 24.9; ESI-MS m/z 417.2 ([M + Na]⁺). Anal. calcd. for C₂₂H₃₄O₆: C, 66.98, H, 8.69; found C, 67.00, H, 8.86.

(4*R*,5*S*,6*R*)-4-(Dimethyl-*tert*-butylsilyloxy)-5,6-(isopropylidendioxy)-7-bezyloxy-heptanyl 2,2-dimethylpropionate (14). 2,6-Lutidine (0.49 cm³, 4.16 mmol) was added to a solution of 13 (821 mg, 2.08 mmol) in dry CH_2Cl_2 (10 cm³) stirred at 0 °C, followed by TBSOTf (0.72 cm³, 3.12 mmol). The mixture was stirred at the same temperature for 1 h before being diluted with EtOAc, washed with water and brine, and dried over anhydrous Na₂SO₄. Removal of the solvent by rotary evaporation and column chromatography (8:1 PE: Et₂O) on silica gel gave 14 (1.048 g, 2.07 mmol, 99%) as a colorless oil: $[\alpha]_{D}^{23}$ +21.03 (c 2.10, CHCl₃). FT-IR (film) v_{max}: 3064, 3030, 2954, 2928, 2856, 1731, 1479, 1461, 1379, 1251, 1154, 1101, 834, 777, 698 cm⁻¹; ¹H NMR (300 MHz, $CDCl_3$): δ 7.39-7.22 (m, 5H), 4.57 (d, J = 12.0 Hz, 1H), 4.48 (d, J =11.9 Hz, 1 H), 4.22 (dd, J = 5.8, 11.2 Hz, 1H), 4.05-3.89 (m, 3H), 3.71 (dt, J = 2.4, 7.9 Hz, 1H), 3.57 (dd, J = 5.7, 9.7 Hz, 1H), 3.43 (dd, J = 6.0, 9.8 Hz, 1H), 1.86-1.71 (m, 1H), 1.73-1.52 (m, 3H),1.41 (s, 3H), 1.32 (s, 3H), 1.18 (s, 9H), 0.85 (s, 9H), 0.05 (s, 3H), 0.03 (s, 3H); ¹³C NMR (75 MHz, CDCl₃): δ 178.5, 137.8, 128.4, 127.8, 108.1, 80.3, 76.0, 73.4, 70.8, 69.1, 64.3, 38.7, 30.7, 27.9, 27.2, 26.0, 25.4, 25.1, 18.3, -4.0, -4.6; ESI-MS m/z 531.4 ([M + Na]⁺); MALDI-HRMS calcd for $C_{28}H_{48}O_6SiNa$ ([M + Na]⁺): 531.31124; found 531.3125.

(4R,5S,6R)-4-(Dimethyl-tert-butylsilyloxy)-5,6-(isopropylidendioxy)-7-hydroxy-heptanyl 2,2-dimethylpropionate (15). A mixture of 14 (852 mg, 1.67 mmol) and Pd(OH)₂ (320 mg) in EtOH (10 cm^3) was stirred under H₂ (1 atm) for 7 h. The solids were filtered off. The filtrate was concentrated on a rotary evaporator. The residue was chromatographed (7:1 PE: EtOAc) on silica gel to afford 15 (564 mg, 1.35 mmol, 81%) as a colorless oil: M.p. 63-65 °C. $[\alpha]_{D}^{24}$ +45.28 (c 3.20, CHCl₃). FT-IR (film) v_{max} : 3277, 2855, 1724, 1481, 1370, 1291, 1003, 721, 661 cm⁻¹; ¹H NMR (300 MHz, CDCl₃): δ 4.14 (dt, J = 6.2, 11.9 Hz, 1H), 4.11-4.01 (m, 3H), 3.79 (dt, J = 3.0, 8.0 Hz, 1H), 3.61 (t, J = 5.9 Hz, 2H), 2.28 (t, JJ = 6.0 Hz, 1H), 1.93-1.51 (m, 4H), 1.47 (s, 3H), 1.35 (s, 3H), 1.18 (s, 9H), 0.88 (s, 9H), 0.09 (s, 3H), 0.07 (s, 3H); ¹³C NMR (75 MHz, CDCl₃): δ 178.5, 108.3, 80.0, 77.5, 70.6, 64.0, 61.4, 38.7, 30.4, 28.0, 27.1, 25.9, 25.8, 25.3, 18.3, -4.1, -4.7; ESI-MS m/z 441.3 ([M + Na]⁺); MALDI-HRMS calcd for C₂₁H₄₂O₆SiNa ([M + Na]⁺): 441.26429; found 441.2645.

(4R,5S,6S)-4-(Dimethyl-tert-butylsilyloxy)-5,6-(isopropylidendioxy)-7-chloro-heptanyl 2,2-dimethylpropionate (16). A mixture of 15 (64 mg, 0.15 mmol), Ph₃P (100 mg, 0.38 mmol) and K₂CO₃ (42 mg, 0.31 mmol) in CCl_4 (1.5 cm³) was refluxed with stirring overnight. The solvent was removed by rotary evaporation. The residue was chromatographed (25:1 PE: EtOAc) on silica gel to give 16 (46 mg, 0.11 mmol, 69%) as a colorless oil: $[\alpha]_{D}^{27}$ +38.93 (c 0.65, CHCl₃). ¹H NMR (300 MHz, CDCl₃): δ 4.22 (dt, J = 8.0, 5.2 Hz, 1 H), 4.12-4.00 (m, 3 H), 3.79 (dt, J = 2.9, 8.2 Hz, 1H), 3.61(dd, J = 4.6, 11.4 Hz, 1H), 3.50 (dd, J = 8.2, 11.5 Hz, 1H), 1.94-1.39 (m, 4H), 1.49 (s, 3H), 1.36 (s, 3H), 1.20 (s, 9H), 0.89 (s, 9H), 0.10 (s, 3H), 0.09 (s, 3H); ¹³C NMR (75 MHz, CDCl₃): δ 178.5, 108.7, 80.4, 77.4, 70.3, 63.9, 43.4, 38.7, 30.7, 27.9, 27.2, 25.9, 25.3, 25.0, 18.3, -4.0, -4.5; FT-IR (film) v_{max}: 2958, 2930, 2857, 1731, 1480, 1381, 1284, 1254, 1222, 1157, 836, 778 cm⁻¹; ESI-MS m/z 459.3 ($[M + Na]^+$); ESI-HRMS calcd for C₂₁H₄₁O₅SiNaCl ([M +Na]⁺) 459.23040; found 459.23056.

(4*R*,5*S*)-4-(Dimethyl-*tert*-butylsilyloxy)-6-oxo-heptanyl 2,2dimethylpropionate (18). *n*-BuLi (1.6 M in hexanes, 0.69 cm³, 1.10 mmol) was added to a solution of i-Pr₂NH (0.15 cm³, 1.10 mmol) in dry THF (2 cm³) and stirred at -78 °C under argon. The mixture was stirred at the same temperature for 1 h. A solution of 16 (87 mg, 0.20 mmol) in dry THF (1 cm³) was introduced. The bath was allowed to warm slowly (over ca. 6 h) to 0 °C before being re-cooled to -78 °C. The mixture was partitioned between EtOAc and aq. sat. NH₄Cl. The phases were separated. The organic layer was washed with water and brine before being dried over anhydrous Na₂SO₄. Removal of the solvent by rotary evaporation and column chromatography (20:1 PE: Et_2O) on silica gel gave 18 (38 mg, 0.105 mmol, 53%) as a colorless oil: $[\alpha]_{D}^{28}$ +49.94 (*c* 0.90, CHCl₃). FT-IR (film) v_{max} : 3477, 2958, 2931, 2859, 1728, 1481, 1463, 1362, 1285, 1256, 1158, 1088, 837, 777 cm⁻¹; ¹H NMR (300 MHz, CDCl₃): δ 4.13-3.94 (m, 4 H), 3.51 (d, J = 6.3 Hz, OH, 1 H), 2.28 (s, 3H), 1.78-1.52 (m, 3H),1.41-1.28 (m, 1H), 1.19 (s, 9H), 0.89 (s, 9H), 0.10 (s, 3H), 0.09 (s, 3H); ¹³C NMR (125 MHz, CDCl₃): δ 209.6, 178.5, 79.2, 73.1, 63.9, 38.7, 29.4 (2'C), 27.2, 25.8, 25.2, 18.0, -4.4, -4.6; ESI-MS m/z 383.2 ([M + Na]⁺); ESI-HRMS calcd for C₁₈H₃₇O₅Si ([M + H]⁺): 361.24048; found 361.24033.

(4R,5S,6R)-4-(Methoxymethyloxy)-5,6-(isopropylidendioxy)-7-benzyloxy-heptanyl 2,2-dimethylpropionate (21). MOMCl (0.18 cm³, 2.37 mmol) was added to a solution of NaI (267 mg, 1.78 mmol) in dry MeO(CH₂)₂OMe (1 cm³) stirred at ambient temperature. The stirring was continued for 10 min before *i*-Pr₂NEt (0.45 cm³, 2.61 mmol) was introduced. A solution of 13 (234 mg, 0.59 mmol) in dry MeO(CH₂)₂OMe (2 cm³) was then added. The mixture was heated to reflux overnight. After being cooled to ambient temperature, the mixture was diluted with EtOAc, washed with aq. sat. NH₄Cl, water and brine, and dried over anhydrous Na₂SO₄. Removal of the solvent by rotary evaporation and column chromatography (20:1 PE: EtOAc) on silica gel gave 21 (176 mg, 0.40 mmol, 68%) as a colorless oil: $[\alpha]_{D}^{23}$ +59.63 (c 0.90, CHCl₃). FT-IR (film) v_{max}: 3031, 2980, 2934, 1727, 1496, 1480, 1455, 1398, 1380, 1369, 1284, 1249, 1220, 1159, 1100, 1031, 738, 699 cm⁻¹; ¹H NMR (300 MHz, CDCl₃): δ 7.39-7.24 (m, 5H), 4.85 (d, J = 7.0 Hz, 1H), 4.63 (d, J = 6.6 Hz, 1H), 4.53 (s, 2H), 4.23 (dd, J = 5.8, 11.6 Hz, 1H), 4.14 (dd, J = 5.6, 8.4 Hz)1H), 4.05-3.86 (m, 2 H), 3.66 (dt, J = 2.6, 7.8 Hz, 1 H), 3.56 (dd, J = 6.4, 9.7 Hz, 1H), 3.44 (dd, J = 5.8, 10.0 Hz, 1H), 3.38 (s, 3H), 1.91-1.70 (m, 1H), 1.68-1.44 (m, 3H), 1.42 (s, 3H), 1.35 (s, 3H), 1.18 (s, 9H). ESI-MS m/z 461.4 ([M + Na]⁺); MALDI-HRMS calcd for $C_{24}H_{38}O_7Na$ ([M + Na]⁺): 461.25098; found 461.2514.

(4*R*,5*S*,6*R*)-4-(Methoxymethyloxy)-5,6-(isopropylidendioxy)-7hydroxy-heptanyl 2,2-dimethylpropionate (22). A mixture of 21 (128 mg, 0.29 mmol) and Pd(OH)₂ (25 mg) in EtOH (4 cm³) was stirred under H₂ (1 atm) for 7 h. The catalyst was filtered off. The filtrate was concentrated on a rotary evaporator and the residue was chromatographed (3:1 PE:EtOAc) on silica gel to afford 22 (105 mg, 0.29 mmol, 100%) as a colorless oil: $[\alpha]_{D}^{22}$ +65.83 (*c* 1.40, CHCl₃). FT-IR (film) v_{max} : 3488, 2961, 2936, 1728, 1481, 1460, 1380, 1370, 1286, 1249, 1221, 1161, 1034 cm⁻¹; ¹H NMR (300 MHz, CDCl₃): δ 4.86 (d, *J* = 7.0 Hz, 1H), 4.66 (d, *J* = 6.5 Hz, 1H), 4.23-4.04 (m, 4H), 3.73 (dt, *J* = 3.6, 7.6 Hz, 1H), 3.62 (t, *J* = 5.9 Hz, 2H), 3.40 (s, 3H), 2.24 (t, *J* = 6.2 Hz, OH, 1H), 1.92-1.50 (m, 4H), 1.48 (s, 3H), 1.36 (s, 3H), 1.19 (s, 9H); ESI-MS *m/z* 371.3 ([M + Na]⁺); MALDI-HRMS calcd for C₁₇H₃₂O₇Na ([M + Na]⁺): 371.20403; found 371.2049.

2-((3aS,4R,6aR)-2,2-Dimethyl-tetrahydrofuro[3,4-d][1,3]dioxol-4-yl)-propyl 2,2-dimethylpropionate (24). A mixture of 22 (72 mg, 0.21 mmol), Ph₃P (136 mg, 0.52 mmol) and K₂CO₃ (58 mg, 0.42 mmol) in CH₂Cl₂-CCl₄ (1:4 v/v, 2 cm³) was refluxed with stirring overnight. The solvent was removed by rotary evaporation. The residue was chromatographed (12:1 PE: EtOAc) on silica gel to give 24 (48 mg, 0.17 mmol, 80%) as a colorless oil: $[\alpha]_{D}^{23}$ -30.82 (c 0.82, CHCl₃). FT-IR (film) v_{max}: 2975, 2933, 2853, 1728, 1481, 1459, 1380, 1371, 1284, 1208, 1162, 1101, 1073, 862 cm⁻¹; ¹H NMR $(500 \text{ MHz}, \text{CDCl}_3)$: $\delta 4.76 (dd, J = 3.8, 6.1 \text{ Hz}, 1\text{H}), 4.57 (dd, J = 3.8, 6.1 \text{ Hz}, 1\text{H})$ 3.7, 6.0 Hz, 1H), 4.17-4.04 (m, 2H), 3.99 (d, J = 10.7 Hz, 1H), 3.44 (dd, J = 3.7, 10.8 Hz, 1H), 3.42-3.37 (m, 1H), 1.86-1.71 (m, 4H), 1.47 (s, 3H), 1.36 (s, 3H), 1.20 (s, 9H); 13C NMR (125 MHz, CDCl₃): *δ* 178.6, 112.0, 82.2, 81.2, 81.0, 72.6, 64.2, 38.7, 27.2, 26.0, 25.4, 24.9 (2'C); ESI-MS m/z 309.2 ([M + Na]+); ESI-HRMS calcd for $C_{15}H_{26}O_5Na$ ([M + Na]⁺): 309.16725; found 309.1669.

(4R,5S,6R)-4-(Methoxymethyloxy)-5,6-(isopropylidendioxy)-7-(p-tosyloxy)-heptanyl 2,2-dimethylpropionate (25). To a solution of alcohol 22 (28 mg, 0.08 mmol) in dry CH₂Cl₂ (1 cm³) stirred at 0 °C were added in turn Et₃N (0.017 cm³, 0.12 mmol), p-TsCl (18 mg, 0.096 mmol), and DMAP (1 mg, 0.008 mmol). The mixture was stirred at ambient temperature overnight. EtOAc was added, followed by aq. sat. NH₄Cl. The phases were separated. The organic layer was washed with water and brine before being dried over anhydrous Na₂SO₄. Removal of the solvent by rotary evaporation and column chromatography (6:1 PE:EtOAc) on silica gel gave tosylate 25 (37 mg, 0.074 mmol, 92%) as a colorless oil: $[\alpha]_{D}^{27}$ +53.62 (c 0.95, CHCl₃). FT-IR (film) v_{max} : 2960, 1728, 1598, 1481, 1368, 1285, 1190, 1178, 1097, 1035, 973, 815, 665 cm⁻¹; ¹H NMR (300 MHz, CDCl₃): δ 7.81 (d, J = 8.4 Hz, 2H), 7.36 (d, J = 8.0 Hz, 2H), 4.79 (d, J = 7.0 Hz, 1H), 4.62 (d, J = 7.2 Hz, 1H), 4.24 (dd, J = 5.8, 11.6 Hz, 1H), 4.19-3.99 (m, 4H), 3.95 (dd, *J* = 6.5, 10.2 Hz, 1H), 3.62 (dt, *J* = 3.9, 7.4 Hz, 1H), 3.38 (s, 3H), 2.46 (s, 3H), 1.91-1.44 (m, 4H), 1.31 (s, 6H), 1.20 (s, 9H); ESI-MS m/z 525.4 ([M + Na]⁺); ESI-HRMS calcd for C₂₄H₃₈O₉SNa ([M + Na]⁺): 525.21287; found 525.21305.

(4R,5R)-4,5-Diethynyl-2,2-dimethyl-[1,3]dioxolane (27). DIBAL-H (1 M in cyclohexane, 13 cm³, 13 mmol) was added to a solution of 26 (1.418 g, 6.50 mmol) in dry toluene (28 cm³) and stirred at -78 °C under argon. After completion of the addition, the mixture was stirred at the same temperature for 2 h when a solution (already stirred at 0 °C for 5 min) of $MeC(O)C(N_2)P(O)(OMe)_3$ (3.740 g, 19.5 mmol) and K_2CO_3 (3.588 g, 26 mmol) in anhydrous MeOH (100 cm³) was introduced dropwise. The cooling bath was allowed to warm naturally while the stirring was continued overnight. The mixture was diluted with EtOAc, washed with aq. sat. NH₄Cl, water and brine, and dried over anhydrous Na₂SO₄. Removal of the solvent by rotary evaporation and column chromatography (6:1 PE:Et₂O) on silica gel gave 27 (529 mg, 3.53 mmol, 54%) as a white solid: M.p. 51–53 °C. $[\alpha]_{D}^{26}$ +81.29 (c 0.96, CHCl₃). FT-IR (film) v_{max} : 3267, 2989, 2939, 2929, 2857, 2125, 1735, 1457, 1382, 1240, 1055, 870 cm⁻¹; ¹H NMR (300 MHz, CDCl₃): δ 4.65 (s, 2 H), 2.57 (s, 2 H), 1.47 (s, 6 H); ¹³C NMR (75 MHz, CDCl₃): δ 112.0, 79.0, 75.3, 70.8, 26.4; EI-MS m/z (%) 135 (M–CH₃⁺, 6.18), 96 (9), 53 (12), 43 (100), 41 (17). Anal. calcd. for $C_9H_{10}O_2$: C, 71.98, H, 6.71. Found: C, 71.68, H, 6.93.

Ethyl ((4R,5R)-5-ethynyl-2,2-dimethyl-[1,3]dioxolan-4-yl)propynoate (28). *n*-BuLi (2.5 M, in hexanes, 1.4 cm³, 3.45 mmol) was added to a solution of 27 (517 mg, 3.45 mmol) in dry THF (35 cm³) stirred at -78 °C under argon. The stirring was continued for 30 min. The cooling bath was allowed to warm slowly to 0 °C (ca. 2 h) and at that temperature for 1 h. The bath was re-cooled to -78 °C. ClCO₂Et (299 mg, 2.76 mmol) was added. The mixture was stirred at the same temperature for 4 h, diluted with EtOAc, washed with aq. sat. NH₄Cl, water and brine, and dried over anhydrous Na₂SO₄. Removal of the solvent by rotary evaporation and column chromatography (40:1 PE:Et₂O) on silica gel gave 28 (302 mg, 1.35 mmol, 49%) as a colorless oil along with recovered starting 27 (300 mg, 2.00 mmol, 58%). Data for 28: $[\alpha]_{D}^{24}$ +116.58 (c 1.00, CHCl₃). FT-IR (film) v_{max} : 3285, 2990, 2939, 2245, 2123, 1716, 1455, 1384, 1246, 1160, 1058, 845, 751 cm⁻¹; ¹H NMR (300 MHz, CDCl₃): δ 4.79 (d, J = 5.8 Hz, 2H), 4.76 (dd, J = 1.7, 6.0 Hz, 1H), 4.24 (q, J = 7.2 Hz, 2H), 2.60 (d, J = 1.3 Hz, 1H), 1.50 (s, 3H), 1.49 (s, 3H), 1.31 (t, J = 7.1 Hz,3H); ¹³C NMR (75 MHz, CDCl₃): δ 152.8, 112.8, 81.7, 78.9, 77.9, 75.7, 70.7, 70.4, 62.4, 26.5, 26.4, 13.9. EI-MS m/z (%) 222 (M⁺, 0.01), 207 (100), 168 (19), 165 (34), 123 (26), 119 (32), 96 (41), 53 (28), 43 (97); EI-HRMS calcd for C₁₂H₁₄O₄ (M⁺) 222.0892; found 222.0894.

Ethyl ((4R,5R)-5-ethynyl-2,2-dimethyl-[1,3]dioxolan-4-yl)propanoate (29). NaBH₄ (247 mg, 6.50 mmol) was added quickly in one portion to a mixture of 28 (288 mg, 1.30 mmol) and CuCl (96 mg, 0.97 mmol) in anhydrous MeOH (26 cm³) stirred at -50 °C. The mixture was stirred at the same temperature for 3 h. EtOAc was added, followed by aq. sat. NH₄Cl. The phases were separated. The organic layer was washed with water and brine before being dried over anhydrous Na₂SO₄. Removal of the solvent by rotary evaporation and column chromatography (20:1 PE: EtOAc) on silica gel gave 29 (263 mg, 1.16 mmol, 89%) as a colorless oil: $[\alpha]_{D}^{25}$ +15.66 (c 1.05, CHCl₃). FT-IR (film) v_{max} : 3271, 2987, 2935, 2114, 1736, 1456, 1373, 1248, 1072, 872 cm⁻¹; ¹H NMR (300 MHz, CDCl₃): δ 4.24 (dd, J = 2.1, 7.7 Hz, 1H), 4.15 (q, J = 7.1 Hz, 2H), 4.07 (ddd, J = 4.6, 7.6, 7.6 Hz, 1H), 2.59-2.34 (m, 3H), 2.13-1.99 (m, 1H), 1.98-1.84 (m, 1H), 1.46 (s, 3H), 1.41 (s, 3H), 1.27 (t, J = 7.1 Hz, 3H); ¹³C NMR (75 MHz, CDCl₃): δ 172.8, 110.2, 80.5, 80.3, 74.9, 70.0, 60.5, 30.3, 27.3, 27.0, 26.1, 14.2. ESI-MS m/z 249.1 ([M + Na]+); EI-HRMS calcd for C₁₂H₁₈O₄ (M⁺): 226.1205; found 226.1203.

(4R,5R)-4,5-Dihydroxy-hept-6-yne-1,4-lactone (30). A solution of **29** (115 mg, 0.51 mmol) and aq. F_3CCO_2H (50% v/v, 0.73 cm³) in CH₂Cl₂ (8 cm³) was stirred at ambient temperature overnight. EtOAc was added, followed by aq. sat. NaHCO₃. The phases were separated. The organic layer was washed with water and brine, and dried over anhydrous Na₂SO₄. The solvent was removed on a rotary evaporator. The residue was dissolved in CH₂Cl₂ (8 cm³). To the solution was added *p*-TsOH (monohydrate, 5 mg, 0.026 mmol). The solution was stirred at ambient temperature overnight. Removal of the solvent by rotary evaporation and column chromatography (2:1 PE: EtOAc) on silica gel gave 30 (62 mg, 0.44 mmol, 87%) as a colorless oil: $[\alpha]_{D}^{29}$ -30.10 (c 0.37, CHCl₃). FT-IR (film) v_{max}: 3407, 3271, 2960, 2927, 2852, 2122, 1743, 1459, 1184, 1047 cm⁻¹; ¹H NMR (300 MHz, CDCl₃): δ 4.67-4.57 (m, 1H), 4.54-4.45 (m, 1H), 2.93 (d, J = 5.0 Hz, 1H), 2.75-2.48 (m, 3H), 2.46-2.14 (m, 2H); ¹³C NMR (75 MHz, CDCl₃): δ 177.0,

81.3, 80.0, 75.2, 64.2, 28.1, 23.2. EI-MS m/z (%): 140 (M⁺, 0.07), 85 (100), 57 (8), 55 (10); EI-HRMS calcd for C₇H₈O₃ (M⁺): 140.0473; found 140.0472.

(4R,5R)-4-Hydroxy-5-(p-tosyloxy)-hept-6-yne-1,4-lactone (31). To a solution of alcohol 30 (45 mg, 0.32 mmol) in dry CH₂Cl₂ (3 cm³) stirred at 0 °C were added in turn Et₃N (0.089 cm³, 0.64 mmol), p-TsCl (91 mg, 0.48 mmol), and DMAP (12 mg, 0.096 mmol). The mixture was stirred at ambient temperature overnight. EtOAc was added, followed by aq. sat. NH₄Cl. The phases were separated. The organic layer was washed with water and brine before being dried over anhydrous Na₂SO₄. Removal of the solvent by rotary evaporation and column chromatography (2:1 PE: EtOAc) on silica gel gave tosylate 31 (104 mg, 0.32 mmol, 100%) as a white solid: M.p. 116–117 °C. $[\alpha]_{D}^{26}$ –62.50 (c 0.93, CHCl₃). FT-IR (KBr) v_{max}: 3269, 2950, 2130, 1783, 1595, 1369, 1345, 1190, 1178, 938, 833, 810, 699 cm⁻¹; ¹H NMR (300 MHz, CDCl₃): δ 7.83 (d, J = 8.3 Hz, 2H), 7.37 (d, J = 8.0 Hz, 2H), 5.19 (dd, J = 2.4, 4.4 Hz, 1H), 4.69 (dt, J = 7.4, 5.3 Hz, 1H), 2.74-2.20 (m, 8H); ¹³C NMR (75 MHz, CDCl₃): δ 175.8, 145.6, 132.7, 129.9, 128.1, 78.3, 78.0, 74.9, 70.4, 27.5, 22.9, 21.7. ESI-MS m/z 316.9 ([M + Na]⁺); EI-HRMS calcd for C₁₄H₁₄O₅S (M⁺): 294.0562; found 294.0564.

(4R,5S)-4,5-Dihydroxy-hept-6-yne-1,4-lactone (35). A solution of 30 (99 mg, 0.71 mmol), Ph₃P (741 mg, 2.83 mmol), p-NO₂PhCO₂H (473 mg, 2.83 mmol) in THF (10 cm³) was stirred at ambient temperature for 10 min. EtO₂CN=NCO₂Et (0.44 cm³, 2.83 mmol) was added. The mixture was stirred at ambient temperature overnight. Solvent was removed by rotary evaporation. The residue was chromatographed (3:1 PE: EtOAc) on silica gel to give the intermediate ester (205 mg, 0.709 mmol) as a colorless oil. MeOH (12 cm³) was added to the residue. The resulting solution was cooled to -15 °C. With stirring, aq. NaOH (1 N, 0.7 cm³) was added. The mixture was stirred at -15 °C for 30 min. EtOAc was added, followed by aq. sat. NH₄Cl. The phases were separated. The organic layer was washed with water and brine before being dried over anhydrous Na₂SO₄. Removal of the solvent by rotary evaporation and column chromatography (3:1 PE: EtOAc) on silica gel gave 35 (75 mg, 0.54 mmol, 76%) from **30**) as a colorless oil: $[\alpha]_{D}^{27}$ +28.68 (c 0.58, CHCl₃). FT-IR (film) v_{max} : 3407, 3290, 2092, 1739, 1471, 1256, 1091 cm⁻¹; ¹H NMR (300 MHz, CDCl₃): δ 4.72-4.61 (m, 2H), 3.30 (broad, OH, 1H), 2.79-2.62 (m, 1H), 2.60-2.24 (m, 4H); ¹³C NMR (75 MHz, CDCl₃): δ 177.6, 81.3, 79.8, 75.4, 63.7, 28.1, 21.7; EI-MS m/z(%): 140 (M⁺, 0.10), 85 (100); EI-HRMS calcd for C₇H₈O₃ (M⁺): 140.0473; found 140.0470.

(4*R*,5*S*)-4-Hydroxy-5-(*p*-tosyloxy)-hept-6-yne-1,4-lactone (36). To a solution of alcohol 35 (26 mg, 0.19 mmol) in dry CH₂Cl₂ (2 cm³) stirred at 0 °C were added in turn Et₃N (0.052 cm³, 0.37 mmol), *p*-TsCl (53 mg, 0.28 mmol), and DMAP (7 mg, 0.056 mmol). The mixture was stirred at ambient temperature overnight. EtOAc was added, followed by aq. sat. NH₄Cl. The phases were separated. The organic layer was washed with water and brine before being dried over anhydrous Na₂SO₄. Removal of the solvent by rotary evaporation and column chromatography (2:1 PE: EtOAc) on silica gel gave tosylate **25** (37 mg, 0.13 mmol, 68%) as a white solid: M.p. 103–105 °C. $[\alpha]_{D}^{23}$ +45.69 (*c* 0.95, CHCl₃). FT-IR (KBr) v_{max} : 3287, 3041, 2990, 2938, 2124, 1774,

1698, 1600, 1533, 1366, 1180, 935, 821, 674 cm⁻¹; ¹H NMR (300 MHz, CDCl₃): δ 7.80 (d, J = 8.5 Hz, 2H), 7.36 (d, J = 8.0 Hz, 2H), 5.26-5.19 (m, 1H), 4.73-4.63 (m, 1H), 2.69-2.22 (m, 8H); ¹³C NMR (75 MHz, CDCl₃): δ 175.8, 145.6, 132.6, 129.9, 128.1, 78.6, 78.5, 75.0, 70.7, 27.4, 22.1, 21.7; ESI-MS m/z 316.9 ([M + Na]⁺); EI-HRMS calcd for C₁₄H₁₄O₅S (M⁺): 294.0562; found 294.0572.

(*R*)-5-(Hepta-(1a*R*)-1,2-diene-7-trimethylsilyl-4,6-diynyl)-dihydro-furan2-one (32). MeLi·LiBr (*ca.* 1.5 M, 0.67 cm³, 1.0 mmol) was added to a solution of TMSC=C-C=CTMS (194 mg, 1.0 mmol) in dry THF (5 cm³) stirred at -78 °C under argon. The cooling bath was allowed to warm to ambient temperature slowly. The stirring was then continued at ambient temperature for 2 h before a solution of anhydrous ZnBr₂ in dry THF (1.0 M, 1.0 cm³, 1.0 mmol) was introduced. The resulting mixture was stirred at the same temperature for 10 min to give a THF solution of TMSC=C-C=CZnBr (*ca.* 0.14 M).

The above prepared THF solution of TMSC=C-C=CZnBr (0.14 M, 1.5 cm³, 0.21 mmol) was transferred *via* a cannula to a flame-dried flask containing Pd(Ph₃P)₄ (11 mg, 0.010 mmol) and **31** (30 mg, 0.10 mmol) in dry THF (1 cm³) stirred at -78 °C under argon. The bath was allowed to warm slowly to -20 °C (*ca.* 3 h). The mixture was diluted with Et₂O, washed with aq. sat. NH₄Cl, water and brine, before being dried over anhydrous Na₂SO₄. Removal of the solvent by rotary evaporation and column chromatography (2:1 PE:Et₂O) on silica gel gave **32** (16 mg, 0.066 mmol, 64%) as a yellowish oil (which deteriorated quickly on removal of the solvent; from a partially concentrated sample of **32** the following data were acquired: ¹H NMR (300 MHz, CDCl₃) δ 5.68 (d, J = 4.0 Hz, 2H), 5.10-5.00 (m, 1H), 2.69-2.39 (m, 3H), 2.23-2.08 (m, 1H), 0.21 (s, 9H). This sample was mainly used for exploring HPLC separation of the allene axial isomers (*cf.* **37**).

(*R*)-5-(Hepta-(1a*S*)-1,2-diene-7-trimethylsilyl-4,6-diynyl)-dihydro-furan2-one (37). The same procedure for conversion of 31 into 32 given above was adopted. From a partially concentrated sample of 37 the following data were acquired: ¹H NMR (300 MHz, CDCl₃) δ 5.76-5.63 (m, 2H), 5.10-5.00 (m, 1H), 2.72-2.07 (m, 4H), 0.21 (s, 9H). This sample was mainly used as a reference in HPLC analysis of 32.

(S)-5-(Prop-2-ynoyl)-dihydro-furan2-one (42). A mixture of acid 40 (780 mg, 6 mmol) in SOCl₂ (6 cm³) was heated to reflux for 3 h. The volatiles were removed on a rotary evaporator. The residue was dissolved in dry THF (24 cm³). To this solution was added CuCl (18 mg, 0.18 mmol). The mixture was cooled to -78 °C. With stirring, a solution of HC≡CMgCl (0.5 M, in THF, 11.5 cm³, 5.75 mmol) was added over 1 h. The bath was then allowed to warm naturally to -20 °C and the stirring was continued at that temperature for 15 h. The mixture was diluted with EtOAc, washed with aq. sat. NH₄Cl, water and brine, and dried over anhydrous Na₂SO₄. Removal of the solvent by rotary evaporation and column chromatography (2:1 PE: Et₂O) on silica gel gave 42 (240 mg, 1.74 mmol, 31%): $[\alpha]_{D}^{25}$ +6.89 (c 0.57, CHCl₃), 99.0% e.e. as determined by HPLC analysis ($t_{R(Major)} = 22.53 \text{ min}$, $t_{R(Minor)} = 18.13 \text{ min}$) on a CHFT-IRALPAK IC column (0.46 cm × 25 cm) eluting with 70:30 n-hexane: i-PrOH at a flow rate of 0.7 cm³ min⁻¹ with the UV detector set to 214 nm. FT-IR (film) *v*_{max}: 3255, 2961, 2095, 1804, 1686, 1461, 1420, 997 cm⁻¹; ¹H NMR (300 MHz, CDCl₃): δ 5.01-4.94 (m, 1H), 3.57 (s, 1H), 2.69-2.30 (m,

4H); ¹³C NMR (75 MHz, CDCl₃): δ 183.1, 175.5, 84.6, 81.6, 78.4, 26.6, 24.7; EI-MS *m*/*z* (%): 139 (M⁺ + 1, 5), 85 (100); EI-HRMS calcd for C₇H₆O₃ (M⁺): 138.0317; found 138.0318.

(4*S*,5*S*)-4,5-Dihydroxy-hept-6-yne-1,4-lactone (44) and (4*S*,5*R*)-4,5-dihydroxy-hept-6-yne-1,4-lactone (45).

Method A. (R)-2-Me-CBS-oxazaborolidine (1.0 M in toluene, 1.82 cm³, 1.82 mmol) was added dropwise to a solution of **42** (126 mg, 0.91 mmol) in dry THF (9 cm³) stirred at -40 °C under argon, followed by BH₃·Me₂S (2.0 M, in THF, 0.46 cm³, 0.92 mmol). The mixture was stirred at the same temperature for 1 h. EtOH (2 cm³) was added. The stirring was continued for 15 min. Water was added, followed by Et₂O. The phases were separated. The organic layer was washed with water and brine before being dried over anhydrous Na₂SO₄. Removal of the solvent by rotary evaporation and column chromatography (2 : 1 PE : EtOAc) on silica gel gave (*S*,*S*)-alcohol **44** (74 mg, 0.53 mmol, 58.2%) and (*S*,*R*)-alcohol **45** (42 mg, 0.30 mmol, 33.0%).

Method B. The procedure was the same as in Method A, except that (*S*)-2-Me-CBS-oxazaborolidine was utilized instead of (*R*)-2-Me-CBS-oxazaborolidine. From **42** (91 mg, 0.66 mmol) were obtained (*S*,*S*)-alcohol **44** (17 mg, 0.12 mmol, 18.2%) and (*S*,*R*)-alcohol **45** (71 mg, 0.51 mmol, 77.2%).

Method C. NaBH₄ (10 mg, 0.27 mmol) was added in one portion to a solution of **42** (24 mg, 0.174 mmol) and CeCl₃ (57 mg, 0.23 mmol) in MeOH (2 cm³) stirred at ambient temperature. Stirring was continued for 1 h before the mixture was diluted with EtOAc, washed with aq. sat. NH₄Cl, water and brine, and dried over anhydrous Na₂SO₄. Removal of the solvent by rotary evaporation and column chromatography (2:1 PE:EtOAc) on silica gel gave (*S*,*S*)-alcohol **44** (7 mg, 0.050 mmol, 21.7%) and (*S*,*R*)- alcohol **45** (4 mg, 0.029 mmol, 12.6%).

Data for (*S*,*S*)-alcohol **44** (a colorless oil): $[\alpha]_D^{23}$ +37.86 (*c* 1.00, CHCl₃); other data the same as its antipode **30**.

Data for (*R*,*S*)-alcohol **45** (a colorless oil): $[\alpha]_{D}^{23}$ –29.56 (*c* 0.58, CHCl₃); other data the same its antipode **35**.

(4*S*,5*S*)-4-Hydroxy-5-(*p*-tosyl)-hept-6-yne-1,4-lactone (46). Using the same procedure for conversion of 30 into 31 given above, tosylate 46 (270 mg, 0.92 mmol, 90%) was obtained as a white solid from alcohol 44 (143 mg, 1.02 mmol); M.p. 116–117 °C. $[\alpha]_{\rm D}^{22}$ +81.25 (*c* 0.73, CHCl₃); other data the same its antipode 31.

(S)-5-(Hepta-(1aS)-1,2-diene-7-trimethylsilyl-4,6-diynyl)-dihydrofuran2-one (47). The same procedure for conversion of 31 into 32 given above was employed for converting 46 into 47, except that chromatography on silica gel was performed using 2:1 pentane-Et₂O as elutent. The fractions containing 47 were combined and partially concentrated and diluted with CHCl₃. The partial concentration and dilution with CHCl₃ was repeated several times until no pentane-Et₂O could be detected on ¹H NMR. The yield of 47 (obtained from 46 (200 mg, 0.68 mmol)) was determined to be 64% by 1H NMR with methyl 4-iodobenzoate as the internal reference. Data for 47: $[\alpha]_{D}^{22}$ +262.97 (c 0.38, CHCl₃). FT-IR (film) *v*_{max}: 2956, 2921, 2850, 2200, 2101, 1950, 1775, 1249, 1149, 843 cm⁻¹; ¹H NMR (300 MHz, CDCl₃): δ 5.68 (d, J = 4.0 Hz, 2H), 5.10-5.00 (m, 1H), 2.69-2.39 (m, 3H), 2.23-2.08 (m, 1H), 0.21 (s, 9H); ¹³C NMR (75 MHz, CDCl₃): δ 214.4, 175.7, 94.3, 91.0, 87.7, 79.0, 77.0, 76.3, 67.9, 28.1, 27.9, -0.4. EI-MS m/z (%): 244 (M^+ , 11.31), 162 (13), 85 (100); EI-HRMS calcd for $C_{14}H_{16}O_2Si$ (M^+): 244.0920; found 244.0922.

(S)-5-(Hepta-(1aS)-1,2-diene-4,6-diynyl)-dihydro-furan-2-one ((4S,5aS)-1). A solution of AgNO₃ (24 mg, 0.14 mmol) in H₂O (0.5 cm^3) was added to a solution of 47 (estimated to be 29 mg, 0.119 mmol, using the partial concentration-dilution technique to change the solvent and ¹H NMR to measure the quantity) in MeOH (2 cm³) stirred at 0 °C with precaution against light. A yellow precipitate formed. The mixture was stirred at the same temperature for 1 h. Et₂O was added, followed by aq. sat. NaCN and aq. sat. NH₄Cl. The phases were separated. The organic layer was washed three times with water and once with brine before being dried over anhydrous Na₂SO₄. Solvent was removed (not to dryness) by rotary evaporation and the residue was chromatographed (2:1 pentane- CH_2Cl_2) on silica gel to give (4S,5aS)-1. The fractions containing this compound were combined and partially concentrated by rotary evaporation and diluted with CH₂Cl₂. The concentration-dilution was repeated several times until no more pentane was detected on ¹H NMR, giving a solution of (4S,5aS)-1 in CH₂Cl₂. The total amount of (4S,5aS)-1 formed in this run was estimated to be 14 mg (0.081 mmol, 71% from 47) by ¹H NMR with methyl 4-iodobenzoate as the internal reference. Data for (4*S*,5a*S*)-1 (same as natural nemotin): UV (MeOH) λ_{max} 208 (shoulder), 235, 249, 263, 278 nm. $[\alpha]_{D}^{23}$ +356.10 (c 0.20, CH₂Cl₂), (lit.^{1d} $[\alpha]_{D}^{20}$ +350 (c 0.20, CH₂Cl₂)). FT-IR (film) v_{max} : 3257, 2960, 2925, 2854, 2204, 2096, 1953, 1774, 1458, 1261, 1097, 1019, 800 cm⁻¹; ¹H NMR (300 MHz, CD₂Cl₂): δ 5.68-5.58 (m, 2 H), 5.00-4.90 (m, 1 H), 2.54-2.30 (m, 4 H), 2.12-1.96 (m, 1 H); ¹³C NMR (75 MHz, CD₂Cl₂): δ 214.6, 175.8, 94.8, 78.5, 76.4, 75.8, 71.7, 67.9, 67.2, 28.2, 28.1. EI-MS m/z (%): 172 (M⁺) (5.72), 142 (15), 107 (9), 90 (23), 85 (100); EI-HRMS calcd. for $C_{11}H_8O_2$ (M⁺): 172.0524; found 172.0526.

(8S,5aS)-Undeca-1-trimethylsilyl-5,6-diene-8,11-diacetoxy-1,3diyne (48). DIBAL-H (1 M, in cyclohexane, 0.5 cm³, 0.5 mmol) was added to a solution of 47 (10 mg, 0.041 mmol) in CH₂Cl₂ (1 cm³) stirred at -78 °C under argon. After completion of the addition, the bath was allowed to warm naturally to ambient temperature (over ca. 2 h). MeOH (1 cm³) was added, followed by Et₂O and aq. sat. potassium sodium tartrate. The mixture was stirred until it became clear. The phases were separated. The organic layer was washed with water and brine before being dried over anhydrous Na₂SO₄. Solvent was removed (not to dryness) by rotary evaporation and the residue was diluted with CH₂Cl₂ (1 cm^3) . To this solution were added Ac₂O (0.024 cm³, 0.25 mmol), pyridine (0.010 cm³, 0.12 mmol) and DMAP (1 mg). The mixture was stirred at ambient temperature overnight before being diluted with Et₂O, washed with aq. sat. NH₄Cl, water and brine, and dried over anhydrous Na₂SO₄. Removal of the solvent by rotary evaporation and column chromatography (4:1 PE: Et₂O) on silica gel gave diacetate 48 (10 mg, 0.030 mmol, 73%) as a colorless oil: $[\alpha]_{D}^{22}$ +55.90 (c 0.18, CHCl₃), 88.7% d.e. ($t_{R(Major)} = 25.10 \text{ min}$, $t_{R(Minor)} = 27.15$ min) as determined by HPLC on a CHFT-IRALPAK IC column (0.46 cm \times 25 cm) eluting with 95:5 nhexane/i-PrOH at a flow rate of 0.5 cm³ min⁻¹ with the UV detector set to 214 nm. FT-IR (film) v_{max}: 2957, 2923, 2852, 2200, 2096, 1941, 1741, 1736, 1369, 1232, 1020, 846 cm⁻¹; ¹H NMR (300 MHz, $CDCl_3$): δ 5.65-5.51 (m, 2H), 5.36-5.24 (m, 1H), 4.08 (t, J = 5.7 Hz, 2H), 2.08 (s, 3H), 2.07 (s, 3H), 1.83-1.61 (m, 4H), 0.20 (s, 9H); ¹³C

NMR (75 MHz, CDCl₃): δ 214.4, 171.1, 170.2, 94.3, 90.5, 87.7, 77.9, 75.9, 70.4, 68.8, 63.8, 30.5, 24.4, 21.0, 20.9, -0.5; ESI-MS *m*/*z* 355.1 ([M + Na]⁺); ESI-HRMS calcd for C₁₈H₂₄O₄SiNa ([M + Na]⁺): 355.13361; found 355.13318.

(4*S*,5*R*)-4-Hydroxy-5-(*p*-tosyl)-hept-6-yne-1,4-lactone (49). Using the same procedure for conversion of 35 into 36 given above, tosylate 49 (403 mg, 1.37 mmol, 90%) was obtained as a white solid from alcohol 45 (213 mg, 1.52 mmol); M.p. 104–106 °C. $[\alpha]_{D}^{22}$ –58.72 (*c* 0.95, CHCl₃); other data the same as its antipode 36.

(8S,5aR)-Undeca-1-trimethylsilyl-5,6-diene-8,11-diacet-oxy-1, 3-diyne (51). Using the same procedure for the conversion of 31 into 32 given above (with 49 to replace 31) starting from 49 (74 mg, 0.25 mmol), (4S,5aR)-allenediyne 50 was obtained as a solution in CHCl₃ and kept at -20 °C. A portion of this solution (2/3) was dissolved in CH₂Cl₂ (1 cm³). The solution was stirred at -20 °C under argon while DIBAL-H (1 M, in cyclohexane, 0.5 cm³, 0.5 mmol) was added dropwise. After completion of the addition, the bath was allowed to warm naturally to ambient temperature (over ca. 2 h). MeOH (1 cm³) was added, followed by Et_2O and aq. sat. potassium sodium tartrate. The mixture was stirred until it became clear. The phases were separated. The organic layer was washed with water and brine before being dried over anhydrous Na₂SO₄. The solvent was removed (not to dryness) by rotary evaporation and the residue was diluted with CH₂Cl₂ (1 cm³). To this solution were added Ac₂O (0.024 cm³, 0.25 mmol), pyridine (0.010 cm³, 0.12 mmol) and DMAP (1 mg). The mixture was stirred at ambient temperature overnight before being diluted with Et₂O, washed with aq. sat. NH₄Cl, water and brine, and dried over anhydrous Na₂SO₄. Removal of the solvent by rotary evaporation and column chromatography (4:1 PE: Et₂O) on silica gel gave 51 (10 mg, 0.024 mmol, 15% from 49) as a colorless oil: $[\alpha]_{D}^{22}$ -10.54 $(c 0.55, CHCl_3)$, 49.2% d.e. (cf. the details given above for 48). ¹H NMR (300 MHz, CDCl₃): δ 5.63-5.53 (m, 2H), 5.35-5.24 (m, 1H), 4.08 (t, J = 5.9 Hz, 2H), 2.07 (s, 3H), 2.06 (s, 3H), 1.82-1.62 (m, 4H), 0.20 (s, 9H); FT-IR (film): 2957, 2924, 2853, 2199, 2102, 1945, 1741, 1235; ESI-MS m/z 355.1 ([M + Na]⁺); ESI-HRMS calcd for $C_{18}H_{24}O_4SiNa$ ([M + Na]⁺): 355.13361; found 355.13403.

Acknowledgements

Financial support from the National Natural Science Foundation of China (20672129, 20621062, 20772143) and the Chinese Academy of Sciences ("Knowledge Innovation", KJCX2.YW.H08) is gratefully acknowledged.

Notes and references

 (a) F. Kavanagh, A. Hervey and W. J. Robbins, Proc. Natl. Acad. Sci. U. S. A., 1950, 36, 1–7; (b) J. D. Bu'Lock, E. R. H. Jones and P. R. Leeming, J. Chem. Soc., 1955, 4270–4276; (c) J. D. Bu'Lock, E. R. H. Jones, P. R. Leeming and J. M. Thompso, J. Chem. Soc., 1956, 3767– 3771; (d) R. E. Bew, R. C. Cambie, E. R. H. Jones and G. Lowe, J. Chem. Soc. C, 1966, 135–138. For reviews on allenic natural products, see: (e) A. Hoffmann-Röder and N. Krause, Angew. Chem., Int. Ed., 2002, 41, 2933–2935; (f) A. Hoffmann-Röder and N. Krause, Angew. Chem., Int. Ed., 2004, 43, 1196–1216; (g) A. Hoffmann-Röder and N. Krause, in Modern Allene Chemistry, ed. N. Krause and A. S. K. Hashmi, Wiley-VCH, Weinheim, 2004, vol. 1, pp 51-92.

² J. D. Bu'Lock, E. R. H. Jones and P. R. Leeming, J. Chem. Soc., 1955, 4270–4276.

- 3 R. E. Bew, R. C. Cambie, E. R. H. Jones and G. Lowe, J. Chem. Soc. C, 1966, 135–138.
- 4 (a) K. Young, H. Jayasuriya, J. G. Ondeyka, K. Herath, C. Zhang, S. Kodali, A. Galgoci, R. Painter, V. Brown-Driver, R. Yamamoto, L. L. Silver, Y. Zheng, J. I. Ventura, J. Sigmund, S. Ha, A. Basilio, F. Vicente, J. R. Tormo, F. Pelaez, P. Youngman, D. Cully, J. F. Barrett, D. Schmatz, S. B. Singh and J. Wang, Antimicrob. Agents Chemother., 2006, 50, 519-526; (b) J. G. Ondeyka, D. L. Zink, K. Young, R. Painter, S. Kodali, A. Galgoci, J. Collado, J. R. Tormo, A. Basilio, F. Vicente, J. Wang and S. B. Singh, J. Nat. Prod., 2006, 69, 377-380. For synthetic studies on phomallenic acids, see: (c) Y.-J. Jian, C.-J. Tang and Y.-K. Wu, J. Org. Chem., 2007, 72, 4851-4855; (d) Y.-J. Jian, Y. Zhang and Y.-K. Wu, Huaxue. Xuebao. (Acta Chim. Sin., in Chinese), 2008, 66, 1991-1994; (Chem. Abstr. 151: 381047); (e) M. Yoshida, M. Al-Amin and K. Shishido, Synthesis, 2008, 1099-1105; (f) K. Ishigami, T. Kato, K. Akasaka and H. Watanabe, Tetrahedron Lett., 2008, 49, 5077-5079; (g) T. Kato, K. Ishigami, K. Akasaka, H. Watanabe and Hidenori, Tetrahedron, 2009, 65, 6953-6958
- 5 (a) J. S. Yadav, M. C. Chander and B. V. Joshi, *Tetrahedron Lett.*, 1988, 29, 2737–2740; (b) J. S. Yadav, P. K. Deshpande and G. V. M. Sharma, *Tetrahedron*, 1990, 46, 7033–7046.
- 6 W. M. Pearlman, Tetrahedron Lett., 1967, 8, 1663-1664.
- 7 A. R. Yeager and N. S. Finney, *Bioorg. Med. Chem.*, 2004, **12**, 6451–6460.
- 8 (a) S. Ohira, Synth. Commun., 1989, **19**, 561–564; (b) G. J. Roth, B. Liepold, S. G. Müller and H. J. Bestmann, Synthesis, 2004, 59–62.
- 9 See: e. g., E. Piers and R. T. Skerlj, Can. J. Chem., 1994, 72, 2468–2482.
- I0 J. H. Babler, V. P. Liptak and N. Phan, J. Org. Chem., 1996, 61, 416–417.
 M. Narisada, I. Horibe, F. Watanabe and K. Takeda, J. Org. Chem., 1989, 54, 5308–5313.
- 12 R. O. Hutchins, S. R. E. Zipkin, I. M. Taffer, R. Sivakumar, A. Monaghan and E. M. Elisseou, *Tetrahedron Lett.*, 1989, 30, 55–56.

- (a) A. O. King, N. Okukado and E.-i. Negishi, J. Chem. Soc., Chem. Commun., 1977, 683–684; (b) E.-i. Negishi, J. Organomet. Chem., 2002, 653, 34–40. For similar coupling of alkyne-type anions with racemic propargylic tosylates see: (c) S. Gueugnot and G. Linstrumelle, Tetrahedron Lett., 1993, 34, 3853–3856; (d) S. Condon-Gueugnot and G. Linstrumelle, Tetrahedron, 2000, 56, 1851–1858. For related coupling of alkyls with optically active propargylic tosylates, see: (e) O. W. Gooding, C. C. Beard, D. Y. Jackson, D. L. Wren and G. F. Cooper, J. Org. Chem., 1991, 56, 1083–1088; (f) G. Gorins, L. Kulnert, C. R. Johnson and L. J. Marnett, J. Med. Chem., 1996, 39, 4871–4878.
- 14 (a) C. J. Elsevier and P. Vermeer, J. Org. Chem., 1985, 50, 3042–3045; (b) C. J. Elsevier, H. Kleijn, J. Boersma and P. Vermeer, Organometallics, 1986, 5, 716–720.
- 15 J. S. Yadav and P. P. Maniyan, Synth. Commun., 1993, 23, 2731-2742.
- 16 W. Bensch, A. Mosandl and K. Fischer, *Tetrahedron: Asymmetry*, 1993, 4, 655–656.
- 17 W. Albrecht and R. Tressl, *Tetrahedron: Asymmetry*, 1993, 4, 1391–1396.
- 18 T. R. Barbee and Kim F. Albizati, J. Org. Chem., 1991, 56, 6764– 6773.
- 19 G. Cahiez and E. Métais, Tetrahedron: Asymmetry, 1997, 8, 1373-1376.
- 20 S. Senda and K. Mori, Agr. Biol. Chem., 1983, 47, 2595-2598.
- 21 A. L. Gemal and J.-L. Luche, J. Am. Chem. Soc., 1981, 103, 5454-5459.
- 22 (a) E. J. Corey, R. K. Bakshi and S. Shibata, J. Am. Chem. Soc., 1987, 109, 5551–5553; (b) E. J. Corey, R. K. Bakshi, S. Shibata, C.-P. Chen and V. K. Singh, J. Am. Chem. Soc., 1987, 109, 7925–7926; (c) for a recent review: E. J. Corey and C. J. Helal, Angew. Chem., Int. Ed., 1998, 37, 1986–2012.
- 23 H. Kleijn, J. Meijer, G. C. Overbeek and P. Vermeer, *Recl. Trav. Chim. Pay. B (J. R. Neth. Chem. Soc.)*, 1982, **101**, 97–101.
- 24 K. Makotoand and H. Akira, Carbohydr. Res., 1976, 52, 96-101.