Efficient and highly enantioselective formation of the all-carbon quaternary stereocentre of lyngbyatoxin A

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Indole **25**, an advanced intermediate in a projected enantioselective total synthesis of lyngbyatoxin A **1**, was prepared from allylic alcohol **11** in 9 steps and >95% ee, key transformations being the enantiospecific rearrangement of vinyl epoxide **14** and the Hemetsberger–Knittel reaction of azide **24**.

Introduction

The Hawaiian blue–green alga *Lyngbya majuscula* Gomont is implicated in the occasional outbreaks of a severe contact dermatitis commonly known as "swimmers' itch".[1] One of the causative agents for this condition is lyngbyatoxin A **1** (Fig. 1), an alkaloid first isolated in 1979 by Moore and co-workers from the lipid extract of seaweed.[2]

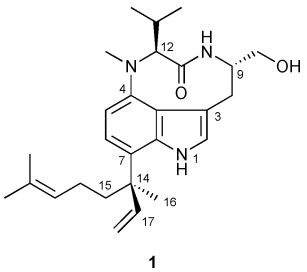
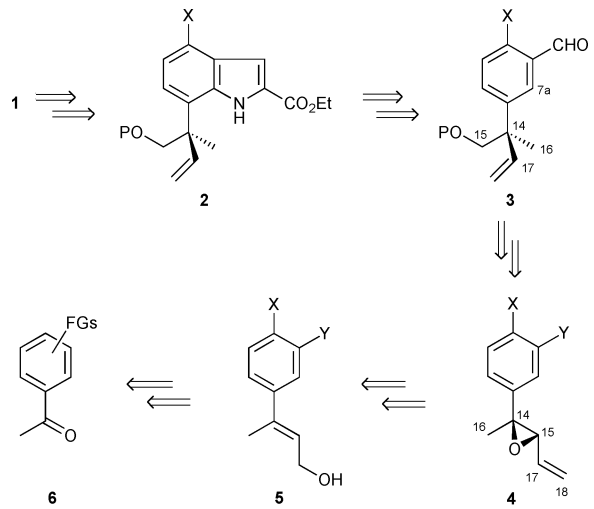


Fig. 1 Structure of lyngbyatoxin A.

Lyngbyatoxin A is also a potent tumor promoter[3] and, like other indolactam alkaloids, exerts its biological activity through activation of protein kinase C (PKC), a family of phosphorylating enzymes involved in the regulation of important cellular processes.[4] Investigation of the structural requirements for the selective activation/inhibition of each PKC isotype is currently an important goal in pharmaceutical research.[5] This interesting biological profile combined with a challenging molecular structure makes lyngbyatoxin A and its analogues worthy targets for the synthetic community.[5,6]

A critical step in any enantioselective approach towards lyngbyatoxin A concerns the installation of the quaternary carbon at C-14.[7,8] We have previously addressed this issue by means of the Jung rearrangement[9] of chiral vinyl epoxides carrying an indole moiety, but this approach was plagued by substantial loss of enantiomeric purity during the rearrangement step.[10] Herein we report a successful (>95% ee) "second generation" approach to this problem, involving epoxide rearrangement *prior* to formation of the indole unit.

According to the simplified retrosynthetic analysis shown in Scheme 1, the target molecule was envisioned to arise from indole **2** *via* functional group manipulation. Key intermediate **2** would be obtained from aldehyde **3** by means of a Hemetsberger–Knittel reaction,[11] while the quaternary carbon stereocentre was planned to be accessed *via* the enantiospecific Jung rearrangement[9] of chiral vinyl epoxide **4**, itself available from allylic alcohol **5** by means of the Sharpless asymmetric epoxidation reaction;[12] a suitably functionalised acetophenone **6** was to be the starting point for the synthesis.



Scheme 1 Simplified retrosynthetic analysis for lyngbyatoxin A.

Results and discussion

After considerable experimentation to determine which functional groups on the aromatic ring would be compatible with the above strategy, the combination X = Br, Y = I (Scheme 1) was chosen.

Since the quaternary centre was planned to be installed by a "chirality transfer" process, the enantiomeric purity of the starting vinyl epoxide is critical, and this was the first issue to be addressed (Scheme 2).

Following a literature procedure,[13] *p*-aminoacetophenone **7** was treated with ICl to afford the corresponding iodinated aniline **8** in good yield. Amine–halogen exchange was then accomplished under Sandmeyer conditions[14] ($NaNO_2$ followed by CuBr, in conc. HBr) to deliver ketone **9** in 86% yield. A Horner–Wadsworth–Emmons reaction[15] with the sodium salt of

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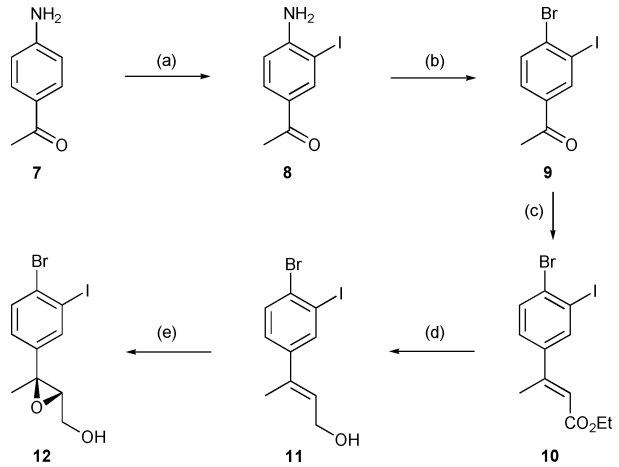
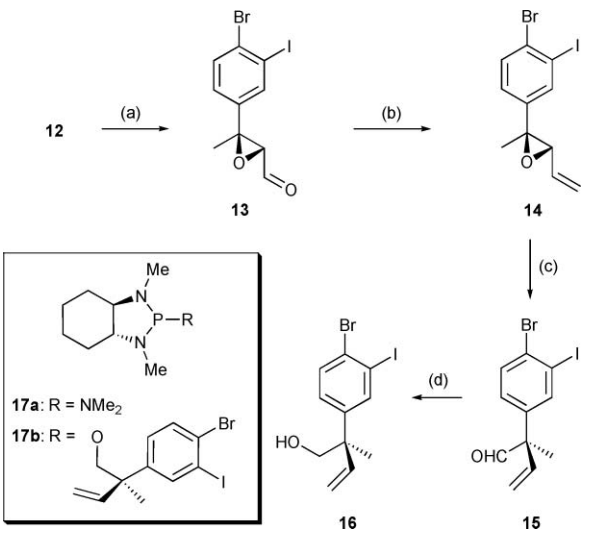


Scheme 2 *Reagents and conditions*: (a) ICl, $CaCO_3$ aq., MeOH, rt, 86%; (b) $NaNO_2$ aq., HBr conc., −10 °C to 0 °C, then CuBr, HBr conc., 80 °C, 86%; (c) NaH, $(EtO)_2P(O)CH_2CO_2Et$, THF, 0 °C to rt, 64%; (d) DIBAL, Et_2O, 0 °C to rt, 96%; (e) L-(+)-DET, 4 Å MS, $Ti(O^iPr)_4$, ^{t}BuOOH, CH_2Cl_2, −20 °C; quant. (crude), 92–94% ee.

triethylphosphonoacetate delivered a mixture of the corresponding E : Z α,β-unsaturated esters in an unoptimised 3.7 : 1 ratio. These isomers could be separated easily by flash chromatography, allowing the isolation of pure *E*-unsaturated ester **10** in 64% yield. Reduction of the ester functionality with DIBAL proceeded uneventfully, providing allylic alcohol **11** in excellent yield. We were then pleased to find that the key asymmetric epoxidation step[12] delivered **12** as a highly crystalline product in essentially quantitative yield and with 92–94% ee, as determined by chiral HPLC. A single recrystallisation from hot hexane–Et_2O 2 : 1 (v : v) yielded material which was enantiomerically pure within the limits of detection.

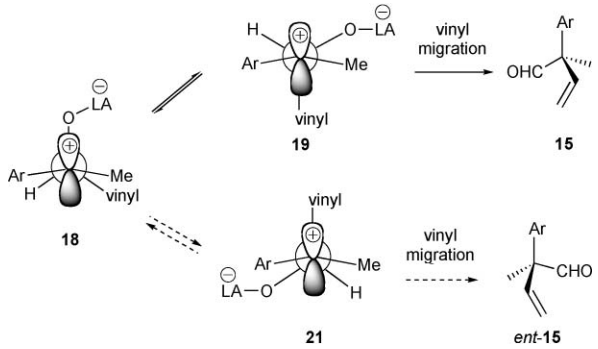
Having secured our first chiral intermediate, we proceeded to investigate the installation of the all-carbon quaternary centre of the target (Scheme 3).[8]



Scheme 3 *Reagents and conditions*: (a) $(COCl)_2$, DMSO then Et_3N, CH_2Cl_2, −78 °C; (b) Ph_3PCH_3Br, KHMDS, THF, 0 °C; (c) $BF_3{\cdot}Et_2O$, CH_2Cl_2, −78 °C, 52% (based on **12**); (d) $NaBH_4$, MeOH, 0 °C to rt, 81%.

Conversion of allylic epoxide **12** to vinyl epoxide **14** was accomplished using the conditions previously reported[9,10] for this type of substrate. Swern oxidation[16] of **12** delivered epoxy aldehyde **13**, which upon Wittig reaction[17] with KHMDS as base gave **14**. Due to the lability of compounds **13** and **14**, these were either used directly or submitted to rapid filtration through a short column of silica gel. Subjection of vinyl epoxide **14** to the conditions developed by Jung for the rearrangement reaction[9] ($BF_3{\cdot}Et_2O$, CH_2Cl_2, −78 °C) delivered aldehyde **15** as the sole product in 52% yield based on **12**. Aldehyde **15** was not suitable for prolonged storage, even at low temperature, so it was routinely subjected to $NaBH_4$ reduction to the corresponding primary alcohol **16**. To determine if the rearrangement had proceeded with complete 1,2-chirality transfer, alcohol **16** was derivatized with the Alexakis reagent **17a**[18] to the phosphorous adduct **17b**. Whereas the ^{31}P-NMR spectrum of racemic **17b**, prepared by MCPBA epoxidation of **11** followed by an identical sequence of steps, showed two peaks of equal intensity at 139.0 and 138.8 ppm, only the higher-field peak was present for **17b** produced *via* the Sharpless epoxidation.

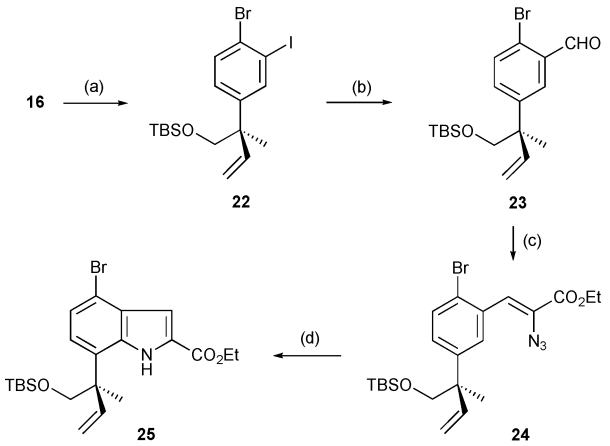
This result implies that the desired vinyl migration in conformer **19**, where the migrating group is correctly aligned with the adjacent vacant p orbital, proceeds significantly faster than conformer equilibration. The latter process would result in the population of conformer **21**, thus leading to vinyl migration onto the enantiotopic face of the planar carbocation and in the undesired formation of *ent*-**15** (Scheme 4).



Scheme 4 Intermediate **18** is formed from **14** and $BF_3{\cdot}Et_2O$, giving **15** *via* conformer **19**.

With the quaternary centre installed in an enantioselective manner, we then attended to the construction of the indole nucleus (Scheme 5).[19]

Treatment of the (crude) primary alcohol **16** with TBSCl and imidazole[20] delivered silyl ether **22** in 80% yield based on **15**. Our annelation strategy calls for a benzaldehyde derivative, and we planned to introduce the required formyl group *via* a regio- and chemo-selective halogen–lithium exchange.[21] Somewhat unexpectedly, this step proved to be very problematic. When the standard conditions for this transformation were used (BuLi, DMF, THF–Et_2O or THF, −100 °C or −78 °C, respectively), only a complex mixture, containing at best trace amounts of the expected aldehyde **22**, was obtained. After extensive model studies with *o*-bromoiodobenzene, we eventually found that when the reaction was carried out in toluene at approximately −100 °C the competing benzyne formation was comparatively slow, and thus the initially formed lithiated species could be successfully trapped



Scheme 5 (a) TBSCl, imid., DMF, rt, 80% (based on **15**); (b) BuLi then DMF, PhMe, approx. −100 °C, 65–71%; (c) $N_3CH_2CO_2Et$, NaOEt, EtOH, −15 °C to −10 °C, 60%; (d) xylene, 140 °C, 69%.

with DMF.[22] Using these conditions, aldehyde **23** was finally obtained reproducibly in 65–71% yield. Subsequent NaOEt-promoted condensation with excess ethyl azidoacetate at low temperature afforded azide **24** in 60% yield, thus setting the stage for the planned Hemetsberger–Knittel reaction.[11] This was accomplished by heating **24** in xylene, which smoothly furnished indole **25** in 69% yield.

Indole **25** is conveniently functionalised so as to allow its conversion into lyngbyatoxin A: the C-3 indolic position is intrinsically nucleophilic,[23] whereas the bromine at C-4 provides a suitable handle for insertion of the amino functionality;[24] furthermore, the TBDMS-protected alcohol moiety will allow the construction of the linalyl appendage (Fig. 2).

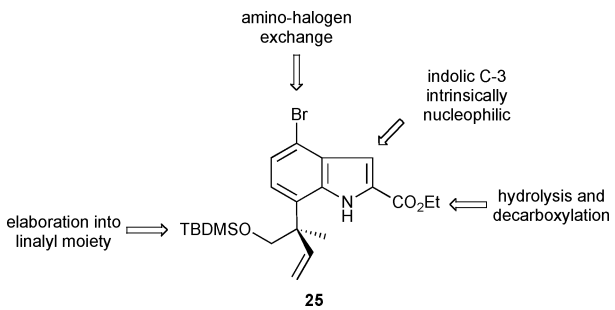


Fig. 2 Planned manipulations to convert indole **25** into lyngbyatoxin A.

Conclusion

The synthesis of enantiomerically pure indole **25**, a late key intermediate in the enantioselective total synthesis of lyngbyatoxin A, was accomplished in 9 steps from the readily available allylic alcohol **11**. The salient features of this route are (i) Sharpless asymmetric epoxidation for initial introduction of chirality, (ii) completely enantiospecific Jung rearrangement of chiral epoxide **14** to install the all-carbon quaternary centre of the target molecule, (iii) formylation of **22** *via* chemo- and regio-selective halogen–lithium exchange, and (iv) clean formation of the indole nucleus through the Hemetsberger–Knittel reaction. To the best of our knowledge, this is the first example of stereocontrolled generation of the characteristic all-carbon quaternary centre of lyngbyatoxin A, thus solving a long-standing problem in the synthesis of this biologically significant alkaloid.

Experimental

General

All moisture- and air-sensitive reactions were carried out under an argon atmosphere using oven-dried or flame-dried glassware. Reaction solvents were distilled prior to use by standard procedures. Et_2O, THF and toluene were distilled under nitrogen from sodium benzophenone. CH_2Cl_2 and NEt_3 were distilled under nitrogen from CaH_2. Anhydrous DMSO and DMF were purchased from Aldrich and stored over 4 Å molecular sieves, under argon. ^{1}H-NMR (300 MHz and 500 MHz) and ^{13}C-NMR (75 MHz) spectra were recorded on either a Varian Mercury 300 (300 MHz) or a Varian Inova 500 (500 MHz) spectrometers at ambient temperature. ^{31}P-NMR (202 MHz) spectra were recorded on a Varian Inova 500 (500 MHz) spectrometer at ambient temperature. Chemical shifts (δ) are reported in ppm. Undeuterated solvent residues were used as internal standard ($CHCl_3$, ^{1}H: 7.27 ppm and ^{13}C: 77.0 ppm). H_3PO_4 (30% aq., 0.0 ppm) was used as external standard for ^{31}P-NMR. Coupling constants (J) are given in Hertz (Hz). Optical rotations were measured with a Perkin Elmer 241 polarimeter at ambient temperature, and the concentration (c) is given in g per 100 mL. Analytical high performance liquid chromatography (HPLC) was performed using a Varian 9012 solvent delivery system with a Varian 9065 polychrome diode array detector. HPLC grade solvents were obtained from LAB-SCAN. Electron impact (EI) low resolution mass spectra (LRMS) were performed with a VG Trio-2 single quadrupole instrument at the Department of Chemistry, Technical University of Denmark. Melting points of crystalline materials were determined on a Heidolph capillary melting point apparatus and are uncorrected. Analytical thin layer chromatography (TLC) analyses were performed using 0.25 mm Merck Kieselgel aluminium-backed 60 F254 silica gel plates. Visualization was achieved by i) exposure to UV light, ii) brief exposure to iodine vapors, iii) dipping into a solution of 5–10% of phosphomolybdic acid in EtOH, and iv) gentle heating. Merck silica gel 60 (40–63 μm, 230–400 mesh) was used for flash chromatography purification. Preparative thin layer chromatography (PTLC) was performed on 20 × 20 cm, 1500 μm glass-backed plates with fluorescent indicator (Aldrich). Microanalyses were performed at the Microanalysis Laboratory, Institute of Physical Chemistry, University of Vienna, Austria. Molecular sieves were dried at 150–160 °C for at least 12 h and then allowed to reach room temperature under argon. Unless otherwise stated, commercially available reagents, purchased from Aldrich, Fluka or Merck, were used without further purification. "Aqueous $\frac{1}{2}$ saturated brine" and "aqueous $\frac{1}{3}$ saturated $NaHCO_3$" refer to a water–brine, 1 : 1 (v : v) and water–saturated $NaHCO_3$, 2 : 1 (v : v) solutions, respectively. The following cooling baths were used: ether–liquid nitrogen (*ca.* −110 to −85 °C); acetone–dry ice (typically for −78 °C but also for temperatures above); *ortho*-dichlorobenzene–liquid nitrogen (*ca.* −25 °C). Commercial NaH (as a 60% dispersion in oil) was washed with pentane (2 portions that cover the amount of NaH dispersion used), and the last traces of pentane were removed under high vacuum.

4-Bromo-3-iodoacetophenone (9). i) Preparation of the diazonium salt. To a suspension of 4-acetyl-2-iodoaniline **8**[13] (8.45 g, 32.3 mmol) in aqueous 47% HBr (77 mL) at −10 °C was added dropwise, over 15 min, a solution of $NaNO_2$ (2.65 g, 38.0 mmol, 1.18 eq.) in water (35 mL). The deep-tan mixture obtained was stirred for 10 min at this temperature, after which the temperature was allowed to increase from −5 °C to 0 °C and stirring continued for a further 1.5 h. The obtained mixture was then kept at ice bath temperature. ii) Sandmeyer reaction. To a vigorously stirred (purple) mixture of CuBr (5.57 g, 38.8 mmol, 1.2 eq.) in aqueous 47% HBr (42 mL) at 60 °C was added portion-wise, over 50 min, the above diazonium suspension (caution: significant frothing occurred during additions), after which the temperature was increased to 80 °C and stirring continued for a further 25 min. The resulting dark mixture was cooled to ice-bath temperature and partitioned between water (400 mL) and EtOAc (400 mL). The aqueous layer was extracted with EtOAc (2 portions of 150 mL) and the combined organic layers were washed with aqueous 1 M HCl (300 mL), aqueous saturated $NaHCO_3$ (200 mL), aqueous $\frac{1}{2}$ saturated brine (250 mL), dried ($MgSO_4$) and concentrated under vacuum to afford a light-tan solid residue which was purified by flash chromatography (hexane–EtOAc, 1 : 1 (v : v)). The title compound was obtained as a pale yellow solid (9.0 g, 86%). R_f (hexane–EtOAc, 1 : 1 (v : v)) 0.55; mp 79–82 °C; ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 8.39 (d, $J = 2.0$ Hz, 1H), 7.76 (dd, $J = 8.2$, 2.0 Hz, 1H), 7.71 (d, $J = 8.2$ Hz, 1H), 2.57 (s, 3H); ^{13}C-NMR ($CDCl_3$, 75 MHz) δ 196.0, 140.3, 137.1, 135.7, 133.1, 129.1, 101.9, 26.8; LRMS (EI) $m/z = 324$ $[M]^+$; Anal. Calcd. for C_8H_6BrIO: C, 29.57; H, 1.86. Found: C, 29.18; H, 2.01.

(*E*)-Ethyl 3-(4-bromo-3-iodophenyl)but-2-enoate (10). To an ice-cold suspension of NaH (766 mg, 31.9 mmol, 1.3 eq.) in THF (45 mL) was added dropwise , over 15 min, a solution of triethylphosphonoacetate (7.16 g, 31.9 mmol, 1.3 eq.) in THF (5 mL) during which gas evolution was observed. The resulting pale yellow solution was stirred at ice bath temperature for 15 min and at room temperature for a further 15 min, after which a solution of 4-bromo-3-iodoacetophenone **9** (7.98 g, 24.6 mmol, 1.0 eq.) in THF (35 mL) was added dropwise at room temperature over 10 min. The dark-tan mixture obtained was stirred at room temperature overnight (for convenience), after which it was partitioned between Et_2O (450 mL) and aqueous $\frac{1}{2}$ saturated brine (500 mL). The aqueous layer was extracted with Et_2O (2 portions of 100 mL) and the combined organic phases were washed with brine (200 mL), dried ($MgSO_4$) and the solvent removed under vacuum to afford a dark tan oil. Purification by (repeated) flash chromatography (hexane–Et_2O, 3 : 1 (v : v)) delivered pure (*E*)- (6.2 g, 64% as a white solid) and (*Z*)-(1.7 g, 17% as a yellow oil) isomers. Combined yield: 81%. For (*E*)-ethyl 3-(4-bromo-3-iodophenyl)but-2-enoate **10**: R_f (hexane–Et_2O, 3 : 1 (v : v)) 0.51; mp 39–42 °C; ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 7.93 (d, $J = 2.2$ Hz, 1H), 7.59 (d, $J = 8.3$ Hz, 1H), 7.28 (dd, $J = 2.2$, 8.3 Hz, 1H), 6.08 (q, $J = 1.3$ Hz, 1H), 4.21 (q, $J = 7.1$ Hz, 2H), 2.50 (d, $J = 1.3$ Hz, 3H), 1.31 (t, $J = 7.1$ Hz, 2H); ^{13}C-NMR ($CDCl_3$, 75 MHz) δ 166.5, 152.8, 142.8, 138.2, 132.8, 130.5, 127.5, 118.6, 101.7, 60.4, 18.0, 14.6; LRMS (EI) $m/z = 394$ $[M]^+$; Anal. Calcd. for $C_{12}H_{12}BrIO_2$: C, 36.49; H, 3.06. Found: C, 36.63; H, 3.15.

(*E*)-3-(4-Bromo-3-iodophenyl)but-2-en-1-ol (11). To an ice-cold solution of (*E*)-ethyl 3-(4-bromo-3-iodophenyl)but-2-enoate **10** (5.83 g, 14.8 mmol, 1.0 eq.) in Et_2O (45 mL) was added dropwise, over 20 min, a solution of DIBAL in toluene (1.0 M, 34.5 mL, 2.3 eq.). The solution obtained was allowed to reach room temperature and stirred for a further 2.5 h, after which it was re-cooled to ice bath temperature, diluted with Et_2O (60 mL) and quenched by careful addition of brine (50 mL). After vigorous stirring for 5 min a gel-type biphasic system formed, to which was then carefully added aqueous 4 M HCl (80 mL), and the mixture was stirred at 0 °C for 10 min and then at room temperature until a clear biphasic system was obtained (typically 20 min). The aqueous layer was extracted with Et_2O (2 portions of 40 mL), the combined organic layers were washed with brine (40 mL), dried ($MgSO_4$) and the solvent removed under vacuum to afford a very pale yellow oil. Purification by flash chromatography (hexane–EtOAc, 1 : 1 (v : v)) afforded the title compound as a white solid (5.0 g, 96%). R_f (hexane–EtOAc, 1 : 1 (v : v)) 0.30; mp 62–64 °C; ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 7.81 (d, $J = 2.2$ Hz, 1H), 7.47 (d, $J = 8.4$ Hz, 1H), 7.15 (dd, $J = 2.2$, 8.4 Hz, 1H), 5.88 (tq, $J = 1.4$, 6.6 Hz, 1H), 4.26–4.30 (m, 2H), 1.94–1.95 (m, 3H); ^{13}C-NMR ($CDCl_3$, 75 MHz) δ 143.6, 137.8, 135.5, 132.5, 128.4, 128.3, 127.1, 101.5, 60.1, 16.1; LRMS (EI) $m/z = 352$ $[M]^+$; Anal. Calcd. for $C_{10}H_{10}BrIO$: C, 34.03; H, 2.86. Found: C, 33.98; H, 2.72.

((2*S*,3*S*)-3-(4-Bromo-3-iodophenyl)-3-methyloxiran-2-yl)methanol (12). To a suspension of powdered 4 Å molecular sieves (472 mg) in CH_2Cl_2 (47 mL) at −25 °C was added dropwise a solution of L-(+)-diethyl tartrate (124 mg, 0.60 mmol, 7.5 mol%) in CH_2Cl_2 (1.5 mL), followed by $Ti(O^iPr)_4$ (117 μL, 0.4 mmol, 5 mol%) and finally a freshly prepared solution of ^{t}BuOOH in toluene[25] (4.2 ml, 15.9 mmol, 2.0 eq.) with 5 min intervals between additions. After 1.5 h at −25 °C, a solution of (*E*)-3-(4-bromo-3-iodophenyl)but-2-en-1-ol **11** (2.8 g, 7.93 mmol, 1.0 eq.) in CH_2Cl_2 (7 mL) was added dropwise over 20 min and stirring continued for a further 4 h at this temperature. The reaction was quenched at −25 °C by addition of aqueous 10% NaOH in brine (0.73 mL) followed by Et_2O (4.5 mL). After stirring at −25 °C for 5 min, this suspension was allowed to reach 5 °C over 10 min, and then $mgSO_4$ (633 mg) and Celite (84 mg) were simultaneously added. After stirring at room temperature for 10 min, the suspension was filtered through a short pad of Celite, and the filtrate was concentrated under vacuum to afford a turbid pale yellow oil which was then taken up in toluene (2 portions of 150 mL) and concentrated under vacuum. The crude product was obtained as a white solid (2.91 g, quantitative, 92–94% ee), which typically was used without further purification. If desired, it can be re-crystallized from hot hexane–Et_2O, 2 : 1 (v : v) (approximately 300 mL) affording the title compound as white needles (2.6 g, 91%, >99% ee). R_f (hexane–EtOAc, 1 : 1 (v : v); double elution) 0.50; mp 59–61 °C; ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 7.75 (d, $J = 2.1$ Hz, 1H), 7.50 (d, $J = 8.3$ Hz, 1H), 7.11 (dd, $J = 2.1$, 8.3 Hz, 1H), 3.88 (dd, $J = 4.4$, 12.2 Hz, 1H), 3.75 (dd, $J = 6.3$, 12.2 Hz, 1H), 2.96 (dd, $J = 4.4$, 6.3, 1H), 1.93 (bs, 1H), 1.59 (s, 3H); ^{13}C-NMR ($CDCl_3$, 75 MHz) δ 143.1, 137.2, 132.7, 129.0, 126.7, 101.5, 66.1, 61.3, 59.9, 17.7; LRMS (EI) $m/z = 368$ $[M]^+$; $[\alpha]_D^{25}$ −9.2 (*c* 2.2, $CHCl_3$); Anal. Calcd. for $C_{10}H_{10}BrIO_2$: C, 32.55; H, 2.73. Found: C, 32.61; H, 2.67. HPLC retention times (R_t): For the (2*S*,3*S*) enantiomer: R_t (OD-H column; hexane–^{i}PrOH, 97 : 3 (v : v); 0.6 mL min^{-1}) = 57.7 min.

***rac*-3-(4-Bromo-3-iodophenyl)-3-methyloxiran-2-yl)methanol (12).** To an ice-cold suspension of commercial MCPBA (722 mg, approximately 3.68 mmol of MCPBA, approximately 1.3 eq.) in CH_2Cl_2 (6 mL) was added dropwise a solution of (*E*)-3-(4-bromo-3-iodophenyl)but-2-en-1-ol **11** (1.0 g, 2.83 mmol, 1.0 eq.) in CH_2Cl_2 (6 mL). The suspension obtained was stirred at ice bath temperature for 15 min and then allowed to reach room temperature, stirred for a further 3.5 h, after which it was re-cooled to −5 °C and filtered through a short pad of Celite. To the pale yellow filtrate obtained was added $Ca(OH)_2$ (80 mg) and this suspension was stirred for 5 min at −5 °C, after which a small portion of Na_2SO_4 was added and stirring was continued for a further 5 min at this temperature. After filtration through a short pad of Celite, the solvent was removed under vacuum to afford a viscous yellow oil which, upon standing under high vacuum, crystallized. Purification by short-column chromatography filtration (silica gel; fast elution; hexane–EtOAc, 1 : 1 (v : v) with 2% NEt_3) afforded the title compound as a white solid (950 mg, 91%). HPLC retention times (R_t): For the (2*R*,3*R*) enantiomer: R_t (OD-H column; hexane–^{i}PrOH, 97 : 3 (v : v); 0.6 mL min^{-1}) = 51.7 min. For the (2*S*,3*S*) enantiomer: R_t (OD-H column; hexane–^{i}PrOH, 97 : 3 (v : v); 0.6 mL min^{-1}) = 57.7 min.

(2*R*,3*S*)-3-(4-Bromo-3-iodophenyl)-3-methyloxirane-2-carbaldehyde (13). A solution of oxalyl chloride (1.78 mL, 20.28 mmol, 2.0 eq.) in CH_2Cl_2 (90 mL) was cooled to −78 °C and treated with a solution of DMSO (2.9 mL, 40.8 mmol, 4.0 eq.) in CH_2Cl_2 (7 mL) over 15 min, during which period gas evolution was observed. After stirring at this temperature for 15 min, a solution of ((2*S*,3*S*)-3-(4-bromo-3-iodophenyl)-3-methyloxiran-2-yl)methanol **12** (3.76 g, 10.19 mmol, 1.0 eq.) in CH_2Cl_2 (25 mL) was added dropwise over a period of 0.5 h, after which a turbid-white mixture was obtained. This mixture was stirred at −78 °C for 0.5 h, after which pre-cooled Et_3N (11.26 mL, 81.52 mmol, 8.0 eq.) was added dropwise over 10 min, and the resulting mixture was then allowed to warm to −30 °C over 1 h. The yellow mixture obtained was poured at this temperature onto hexane (140 mL) and CH_2Cl_2 (200 mL) and gently shaken with pH 7 phosphate buffer (80 mL). The layers were separated and the aqueous layer extracted with CH_2Cl_2 (2 portions of 30 mL). The combined organic layers were washed with aqueous 1 M $KHSO_4$ (2 portions of 150 mL), aqueous $\frac{1}{3}$ saturated $NaHCO_3$ (2 portions of 30 mL), brine (150 mL) and dried (Na_2SO_4). Removal of the solvent under vacuum afforded a thick yellow oil which was crudely purified *via* a short-column chromatography filtration (silica gel; fast elution; hexane–EtOAc, 1 : 1 (v : v) with 2% NEt_3) to afford a thick pale yellow oil that eventually crystallized upon standing in the cold (3.40 g) and was used without further purification. R_f (hexane–EtOAc, 1 : 1 (v : v)) 0.57; ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 9.64, (d, J = 4.0 Hz, 1H), 7.96 (d, J = 2.2 Hz, 1H), 7.73 (d, J = 8.3 Hz, 1H), 7.40 (dd, J = 2.2, 8.3 Hz, 1H), 3.48 (d, J = 4.0, 1H), 1.82 (s, 3H); ^{13}C-NMR ($CDCl_3$, 75 MHz) δ 205.6, 142.2, 137.5, 132.9, 129.2, 127.3, 101.1, 66.2, 62.0, 16.9; LRMS (EI) m/z = 366 [M]$^+$.

(2*R*,3*S*)-3-(4-bromo-3-iodophenyl)-2-methyl-3-vinyloxirane (14). To an ice-cold slurry of methyltriphenylphosphonium bromide (4.97 g, 13.90 mmol, 1.5 eq.) in THF (100 mL) was added a solution of KHMDS in toluene (0.5 M, 24.1 mL, 1.3 eq.) over 15 min. The bright-yellow suspension obtained was allowed to reach room temperature and stirred for a further 1.5 h, after which it was re-cooled to 0 °C and a solution of (crudely purified) (2*R*,3*S*)-3-(4-bromo-3-iodophenyl)-3-methyloxirane-2-carbaldehyde **13** (3.33 g, 9.1 mmol, 1.0 eq.) in THF (17 mL) was then added dropwise over a 10 min period. The tan suspension obtained was allowed to reach room temperature and stirred for a further 1.5 h, after which it was re-cooled to ice bath temperature and filtered through a short Celite pad to afford a deep-red solution. Removal of the solvent under vacuum afforded a tan oil, which was crudely purified by short-column chromatography filtration (silica gel; fast elution; Et_2O) to afford a tan oil that was used without further purification (2.97 g). R_f (hexane–Et_2O, 3 : 1 (v : v)) 0.60; ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 7.84 (d, J = 2.2 Hz, 1H), 7.57 (d, J = 8.3 Hz, 1H), 7.19 (dd, J = 2.2, 8.3 Hz, 1H), 5.82 (sept, J = 7.0, 10.5, 17.3 Hz, 1H), 5.51 (ddd, J = 0.9, 1.4, 17.3 Hz, 1H), 5.44 (ddd, J = 0.8, 1.4, 10.5 Hz, 1H), 3.24 (d, J = 7.0 Hz, 1H), 1.62 (s, 3H); ^{13}C-NMR ($CDCl_3$, 75 MHz) δ 143.4, 137.2, 133.8, 132.7, 132.5, 126.7, 121.7, 121.7, 101.5, 67.0, 61.3, 17.5; LRMS (EI) m/z =364 [M]$^+$.

(*R*)-2-(4-bromo-3-iodophenyl)-2-methylbut-3-enal (15). To a −78 °C cooled solution of (crudely purified) (2*R*,3*S*)-3(4-bromo-3-iodophenyl)-2-methyl-3-vinyloxirane **14** (2.81 g, 7.70 mmol, 1.0 eq.) in CH_2Cl_2 (110 mL) was added $BF_3{\cdot}Et_2O$ (1.1 mL, 8.68 mmol, 1.12 eq.) and the resulting deep-pinkish solution was stirred at this temperature for 10 min, after which it was poured onto Et_2O (300 mL) and aqueous $\frac{1}{3}$ saturated $NaHCO_3$ (200 mL). The layers were separated and the aqueous phase was extracted with Et_2O (2 portions of 60 mL). The combined Et_2O extracts were washed with brine (100 mL), dried (Na_2SO_4) and concentrated to a golden oil, which was then purified by flash chromatography (hexane–Et_2O, 3 : 1 (v : v)) to afford the title compound as a pale yellow oil (1.9 g, 52% based on allylic alcohol **12**) that was either best kept frozen in a benzene matrix under argon or used immediately. R_f (hexane–Et_2O, 3 : 1 (v : v)) 0.47; ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 9.52, (s, 1H), 7.71 (d, J = 2.2 Hz, 1H), 7.60 (d, J = 8.3 Hz, 1H), 7.07 (ddd, J = 0.4, 2.2, 8.3, Hz, 1H), 6.12 (ddd, J = 0.40, 10.7, 17.6 Hz, 1H), 5.46 (d, J = 10.7, 1H), 5.20 (d, J = 17.6, 1H), 1.51 (s, 3H); ^{13}C-NMR ($CDCl_3$, 75 MHz) δ 198.5 141.1, 139.5, 137.4, 133.1, 129.2, 129.0, 118.7, 102.2, 57.4, 20.4; LRMS (EI) m/z = 337 [M − C_2H_3]$^+$; $[\alpha]_D^{25}$ +27.8 (*c* 1.3, $CHCl_3$).

(*R*)-2-(4-Bromo-3-iodophenyl)-2-methylbut-3-en-1-ol (16). A solution of (*R*)-2-(4-bromo-3-iodophenyl)-2-methylbut-3-enal **15** (1.18 g, 3.23 mmol, 1.0 eq.) in MeOH (35 mL) at 0 °C was treated with $NaBH_4$ (114 mg, 3.0 mmol, 0.9 eq.). After stirring for 15 min at ice bath temperature, the solution was allowed to warm to room temperature and stirred for a further 2 h, at which time it was concentrated to half of its initial volume and partitioned between water (15 mL) and Et_2O (50 mL). The aqueous layer was extracted with Et_2O (20 mL) and EtOAc (20 mL) and the combined organic phases were washed with brine (10 mL), dried ($NaSO_4$) and concentrated under vacuum to afford a yellow oil residue which typically was used without further purification. For analytical purposes the crude product was purified by flash chromatography on silica gel (hexane–EtOAc, 1 : 1 (v : v)) (960 mg, 81%). R_f (hexane–EtOAc, 1 : 1 (v : v)) 0.52; ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 7.81 (d, J = 2.3 Hz, 1H), 7.55 (d, J = 8.4 Hz, 1H), 7.20 (dd, J = 2.3, 8.4 Hz, 1H), 5.98 (dd, J = 10.8, 17.6 Hz, 1H), 5.30 (dd, J = 0.9, 10.8, 2H), 5.14 (dd, J = 0.9, 17.6, 1H), 3.74 (s, 2H), 1.38 (s, 3H); ^{13}C-NMR ($CDCl_3$, 75 MHz) δ 145.9, 142.6,

139.3, 132.6, 128.7, 127.9, 115.9, 101.7, 69.7, 46.8, 22.9; LRMS (EI) $m/z = 368$ $[M]^+$.

Determination of the ee of alcohol (16) using the Alexakis reagent. To the Alexakis reagent[18] (0.10 mL of a 0.2 M solution in benzene, 0.02 mmol, 1.1 eq.) was added a solution of (*R*)-2-(4-bromo-3-iodophenyl)-2-methylbut-3-en-1-ol **16** (7.0 mg, 0.018 mmol, 1.0 eq.) in benzene (0.2 mL) and the resulting solution was left stirring at room temperature under argon for 15 h. The resulting solution was then transferred into an NMR tube and approximately 100 μL of C_6D_6 were added for locking. For *rac*-**17**: ^{31}P-NMR (C_6D_6, 202 MHz) δ 139.0 and 138.8 (equal intensities). For **17**: ^{31}P-NMR (C_6D_6, 202 MHz) δ 138.8.

(*R*)-(2-(4-Bromo-3-iodophenyl)-2-methylbut-3-enyloxy)(*tert*-butyl)dimethylsilane (22). To a solution of TBDMSCl (131 mg, 0.89 mmol, 1.3 eq.) and imidazole (122 mg, 1.77 mmol, 2.6 eq.) in DMF (0.65 mL) was added a solution of (crude) (*R*)-2-(4-bromo-3-iodophenyl)-2-methylbut-3-en-1-ol **16** (245 mg, 0.66 mmol, 1.0 eq.) in DMF (1.35 mL) at room temperature. After stirring at this temperature for 7 h, the resulting solution was partitioned between aqueous 1 M HCl (15 mL) and Et_2O (25 mL). The organic layer was washed with a second portion of aqueous 1 M HCl (15 mL) and the combined acidic layers were extracted with Et_2O (10 mL). The combined organic layers were washed with aqueous $\frac{1}{2}$ saturated $NaHCO_3$ (25 mL), brine (15 mL), dried (Na_2SO_4) and concentrated under vacuum to afford a pale yellow residue. Purification by flash chromatography on silica gel (hexane–Et_2O, 3 : 1 (v : v)) delivered the title compound as a clear oil (254 mg, 80% based on **15**). R_f (hexane–Et_2O 3 : 1 (v : v)) 0.69; ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 7.89 (d, $J = 2.2$ Hz, 1H), 7.55 (d, $J = 8.4$ Hz, 1H), 7.23 (dd, $J = 2.2$, 8.4 Hz, 1H), 6.04 (dd, $J = 10.9$, 17.6 Hz, 1H), 5.21 (dd, $J = 1.2$, 10.9 Hz, 1H), 5.10 (dd, $J = 1.2$, 17.6 Hz, 1H), 3.70 (s, 2H), 1.37 (s, 3H), 0.88 (s, 9H), 0.01 (s, 3H), 0.00 (s, 3H); ^{13}C-NMR ($CDCl_3$, 75 MHz) δ 152.3, 148.8, 145.1, 137.5, 134.5, 132.5, 119.7, 106.3, 75.7, 51.9, 31.4, 28.2, 23.8, 0.0; LRMS (EI) $m/z = 482$ $[M]^+$; $[\alpha]_D^{25}$ −10.9 (*c* 2.3, $CHCl_3$).

(*R*)-2-Bromo-5-(2-((*tert*-butyldimethylsilyloxy)methyl)but-3-en-2-yl)benzaldehyde (23). To a −105 °C to −100 °C cooled slurry of (*R*)-(2-(4-bromo-3-iodophenyl)-2-methylbut-3-enyloxy)(*tert*-butyl)dimethylsilane **22** (429 mg, 0.89 mmol, 1.0 eq.) in toluene (14.8 mL) was added a solution of ^{n}BuLi in hexanes (1.6 M, 1.02 mmol, 0.64 mL, 1.15 eq.) over approximately 8 s. After stirring at this temperature for 2 min, DMF (193 μL, 2.49 mmol, 2.8 eq.) was added over 5 s. The resulting pale yellow solution was stirred at −103 °C to −95 °C for 1.5 h and then allowed to reach −40 °C over 0.5 h, after which the cooling bath was replaced by a water bath and stirring was continued for a further 10 min. The resulting pale yellow solution was then partitioned between Et_2O (80 mL) and water (15 mL) and the aqueous layer was extracted with Et_2O (2 portions of 20 mL). The combined organic layers were washed with $\frac{1}{2}$ brine (20 mL), dried (Na_2SO_4) and concentrated under vacuum affording a pale yellow oil residue. Purification by flash chromatography on silica gel (hexane, hexane–Et_2O, 6 : 1 (v : v)) delivered the title compound as a colorless oil (242 mg, 71%). R_f (1st elution, hexane–Et_2O, 6 : 1 (v : v); 2nd elution, hexane) 0.71; ^{1}H-NMR (d-acetone, 300 MHz) δ 10.34 (s, 1H), 7.95 (d, $J = 2.5$ Hz, 1H), 7.73 (d, $J = 8.4$ Hz, 1H), 7.65 (dd, $J = 2.5$, 8.4 Hz, 1H), 6.16 (dd, $J = 10.9$, 17.6 Hz, 1H), 5.23 (dd, $J = 1.2$, 10.9 Hz, 1H), 5.17 (dd, $J = 1.2$, 17.6 Hz, 1H), 3.86 (d, $J = 0.8$ Hz, 2H), 1.45 (s, 3H), 0.84 (s, 9H), 0.02 (s, 3H), 0.00 (s, 3H); ^{13}C-NMR ($CDCl_3$, 75 MHz) δ 191.3, 146.5, 143.6, 135.3, 133.6, 133.1, 129.0, 124.0, 113.9, 70.2, 46.8, 25.5, 22.2, 18.0, −6.2; LRMS (EI) $m/z = 384$ $[M]^+$.

(*R*,*Z*)-Ethyl-2-azido-3-(2-bromo-5-(2-((*tert*-butyldimethylsilyloxy)methyl)but-3-en-2-yl)phenyl)acrylate (24). Sodium metal (35.9 mg, 1.56 mmol, 6.0 eq.) was dissolved in EtOH (1.0 mL). To the resulting solution was slowly added, at −15 °C and over 1 h, a solution of (*R*)-2-bromo-5-(2-((*tert*-butyldimethylsilyloxy)methyl)but-3-en-2-yl)benzaldehyde **23** (100 mg, 0.26 mmol, 1.0 eq.) and ethyl azidoacetate (0.71 mL of a 2.39 M solution in EtOH, 1.69 mmol, 6.5 eq.). During addition a milky pale yellowish suspension formed. The temperature was then allowed to rise from −15 °C to −10 °C and stirring was continued for a further 18 h. The orange suspension obtained was then stirred at room temperature for 0.5 h, re-cooled to ice bath temperature, quenched with aqueous saturated NH_4Cl (0.7 mL) and gently partitioned between Et_2O–EtOAc (1 : 1 (v : v)) (30 mL) and aqueous $\frac{1}{2}$ saturated NH_4Cl (10 mL). The deep-tan aqueous layer was further extracted with Et_2O–EtOAc (1 : 1 (v : v)) (3 portions of 10 mL); the combined organic layers were washed with aqueous $\frac{1}{2}$ saturated brine (10 mL) and dried (Na_2SO_4). The obtained tan solution was then concentrated to approximately 5 mL and filtered through a short column of silica gel (Et_2O). After removal of the solvent under vacuum, a reddish oil was obtained which was purified by PTLC (hexane–Et_2O, 3 : 1 (v : v)). The title compound was obtained as a colourless oil (78 mg, 60%). R_f (1st elution, hexane–Et_2O, 3 : 1 (v : v); 2nd elution, pentane) 0.63 (note: the R_f values for the starting material and the product are very similar); ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 8.14 (d, $J = 2.4$ Hz, 1H), 7.55 (d, $J = 8.5$ Hz, 1H), 7.30 (d, $J = 2.6$ Hz, 1H), 7.23 (dd, $J = 2.6$, 8.5 Hz, 1H), 6.11 (dd, $J = 10.9$, 17.6 Hz, 1H), 5.23 (dd, $J = 1.2$, 10.9 Hz, 1H), 5.13 (dd, $J = 1.2$, 17.6 Hz, 1H), 4.43 (q, $J = 7.1$ Hz, 2H), 3.77 (d, $J = 1.6$ Hz, 2H), 1.46 (t, $J = 7.1$ Hz, 3H; partial overlap with s at $\delta = 1.43$ ppm), 1.43 (s, 3H; partial overlap with s at $\delta = 1.46$ ppm), 0.88 (s, 9H), 0.02 (s, 3H), 0.00 (s, 3H); ^{13}C-NMR ($CDCl_3$, 75 MHz) δ 169.0, 150.6, 149.3, 137.8, 137.7, 136.0, 135.4, 132.7, 129.6, 128.3, 119.5, 76.0, 68.1, 52.3, 31.4, 28.2, 23.9, 19.9, 0.0.

(*R*)-Ethyl-4-bromo-7-(1-*tert*-butyldimethylsilyoxy)-2-methylbut-3-en-2-yl)-1*H*-indole-2-carboxylate (25). A solution of (*R*,*Z*)-ethyl 2-azido-3-(2-bromo-5-(1-*tert*-butyldimethylsilyoxy)-2-methylbut-3-en-2-yl)phenyl)acrylate **24** (74 mg, 0.14 mmol) in *meta*-xylene (1.3 mL) was added dropwise over 1 h to refluxing *meta*-xylene (3.7 mL). The obtained solution was refluxed for a further 3.5 h, after which the solvent was removed under vacuum to afford a tan oil. Purification by PTLC (hexane–Et_2O, 5 : 1 (v : v)) afforded the title compound as a pale yellow oil (45 mg, 69%). R_f (hexane–Et_2O, 5 : 1 (v : v)) 0.27; ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 9.87, (brs, 1H), 7.33 (d, $J = 7.9$ Hz, 1H), 7.28 (d, $J = 2.3$ Hz, 1H), 7.18 (d, $J = 7.9$ Hz, 1H), 6.24 (dd, $J = 10.8$, 17.7 Hz, 1H), 5.40 (dd, $J = 1.1$, 10.8 Hz, 1H), 5.31 (dd, $J = 1.1$, 17.7 Hz, 1H), 4.45 (q, $J = 7.1$ Hz, 2H), 4.02 (d, $J = 10.0$ Hz, 1H), 3.87 (d, $J = 10.0$ Hz, 1H), 1.51 (s, 3H), 1.46 (t, $J = 7.1$ Hz), 0.87 (s, 9 H), 0.01 (s, 3 H), 0.00 (s, 3 H); ^{13}C-NMR ($CDCl_3$, 75 MHz) δ 167.3, 149.3, 141.7, 134.5, 134.0, 133.0, 129.8, 129.0, 120.5, 120.4, 113.9, 76.2,

66.8, 52.3, 31.6, 28,8, 24.1, 20.1, 0.0; LRMS (EI) $m/z = 465$ $[M]^+$; $[\alpha]_D^{25}$ +22.7 (*c* 2.15 in $CHCl_3$).

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