Cryptophycin-39 Unit A Precursor Synthesis by a Tandem Shi Epoxidation and Lactonization Reaction of *trans*-Styryl Acetic Acid

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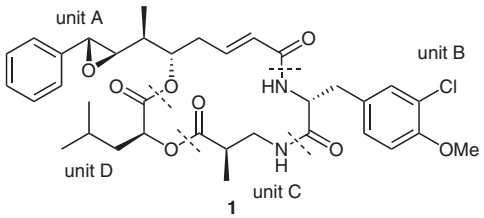
Abstract: Unit A of cryptophycins is a δ-hydroxy acid with two or four stereogenic centers. The first synthesis of the unit A building block of cryptophycin-39 is based on a catalytic asymmetric Shi epoxidation of *trans*-styryl acetic acid followed by an in situ lactonization. The scope of this reaction has been investigated with respect to various β,γ-unsaturated carboxylic acids as substrates for the asymmetric synthesis of 4-hydroxy-5-phenyl-tetrahydrofuran-2-ones under Shi conditions.

Key words: asymmetric synthesis, bioorganic chemistry, epoxidations, lactones, natural products

Cryptophycins are a group of 16-membered macrocyclic depsipeptides which have been isolated from cyanobacteria of the genus *Nostoc* and from the marine sponge *Dysidea arenaria*.[1] This family of natural products with its main member cryptophycin-1 (**1**) is attracting much attention due to their superb cytotoxicity and antitumor activity even against multidrug-resistant tumor cell lines. It often exceeds the activity of vinblastine and paclitaxel.[2] Numerous cryptophycin analogues have been synthesized and their biological activity has been evaluated.[1f,2a]



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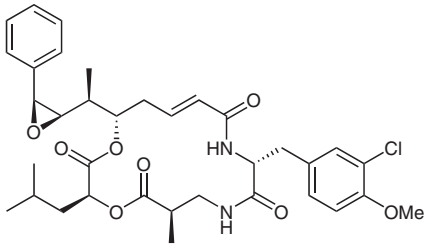

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Figure 1 Structures of cryptophycin-1 (**1**) and cryptophycin-39 (**2**)

Retrosynthetically, cryptophycins can be divided into the respective hydroxy and amino acid building blocks, that is, units A–D (Figure 1). From a synthetic point of view cryptophycin-39 (**2**) is one of the most interesting cryptophycin analogues. It contains a *cis*-epoxide in its unit A and was obtained by Chaganty et al. through a semisynthetic approach. Opening of the epoxide in cryptophycin-1 (**1**) under acidic conditions gives the corresponding chlorohydrin.[3] The chloro-substituted stereogenic center in the benzylic position was then partly epimerized by the addition of excess lithium chloride. After HPLC separation of the diastereomers the epimeric chlorohydrin was converted back to an epoxide function under basic conditions yielding cryptophycin-39 (**2**) on a single-digit milligram scale. It showed moderate bioactivity (IC_{50} 72 nM) against the human upper throat tumor cell line KB.[3]

Several recent papers address the synthesis of cryptophycin-1 unit A precursors containing four stereogenic centers. In many cases the configuration of the future *syn*-epoxide is established by conversion of a *syn*-diol under retention of the configuration.[4] Following this strategy, a six- or seven-step synthesis of a cryptophycin-1 unit A building block was recently published.[5]

However, it had not been known so far, whether the unit A building block of cryptophycin-39 could be obtained following a similar route. Our retrosynthetic analysis suggested to start from (4*R*,5*S*)-4-hydroxy-5-phenyl-tetrahydrofuran-2-one (**5**) as a key intermediate in the synthesis (Scheme 1).

An asymmetric three-step synthetic approach to *ent*-**5** had been published by Kino et al.[6] The first step was based on the enantioselective epoxidation of *trans*-ethyl-3-benzoylacrylate with cumene hydroperoxide and a catalyst derived from lanthanum isopropoxide, tris(4-fluorophenyl)phosphine oxide and BINOL. This was followed by a diastereoselective reduction of the ketone with $Zn(BH_4)_2$, reductive opening, and in situ lactonization with diphenyl diselenide and $NaBH_4$.

In addition, Burrows and Van Horn published a one-step synthesis of *rac*-**5** from commercially available *trans*-styryl acetic acid (**4**) by oxidation with Oxone (potassium monopersulfate triple salt) and in situ lactonization in aqueous acetonitrile solution in very good yield.[7]

Those reaction conditions employed are similar to the ones used in the Shi epoxidation of olefines, a method

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developed by Shi et al. mediated by the D-fructose-derived ketone catalyst **3**.[8] This epoxidation method was also used by Hoard et al. on a late stage to synthesize a cryptophycin derivative.[9] Reports of unsaturated carboxylic acids as starting materials for such an asymmetric in situ lactonization are very rare. To the best of our knowledge, only one Shi epoxidation from the γ,δ-unsaturated potassium *trans*-6-(3-fluorophenyl)-4-hexenoate yielding the corresponding lactone has been published so far.[10]

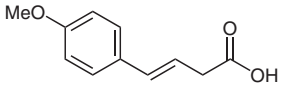
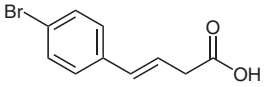
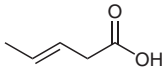
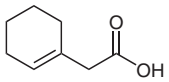
After careful optimization the reaction conditions for substrate **4**, the asymmetric epoxidation gave the desired hydroxy lactone **5**. The enantiomeric excess of the reaction (determined by chiral HPLC) was increased by recrystallization from 82% ee to 90% ee in 44% yield (Table 1, entry 1).[11] For comparison, application of the Shi catalyst **3** under the reaction conditions reported for the racemic synthesis[7] led to an improved yield of 81% but only 50% ee.

The scope of the reaction was further examined. The asymmetric and racemic lactonization of substituted *trans*-styryl acetic acids[12] (Table 1, entries 2 and 3), such as *trans*-*p*-methoxystyryl acetic acid (33% yield, 45% ee) and *trans*-*p*-bromostyryl acetic acid (15% yield, 82% ee) were performed. The reaction of aliphatic β,γ-unsaturated carboxylic acids, such as *trans*-*n*-pent-3-enoic acid and 1-cyclohexene-1-acetic acid (Table 1, entries 4 and 5) did not yield any lactone at all. The limited substrate range is in agreement with the results published by Burrows.[7] The racemic epoxidation of *trans*-cinnamic acid and *p*-vinylbenzoic acid with Oxone gave the corresponding epoxides in only 5% and 30% yield, respectively.[7]

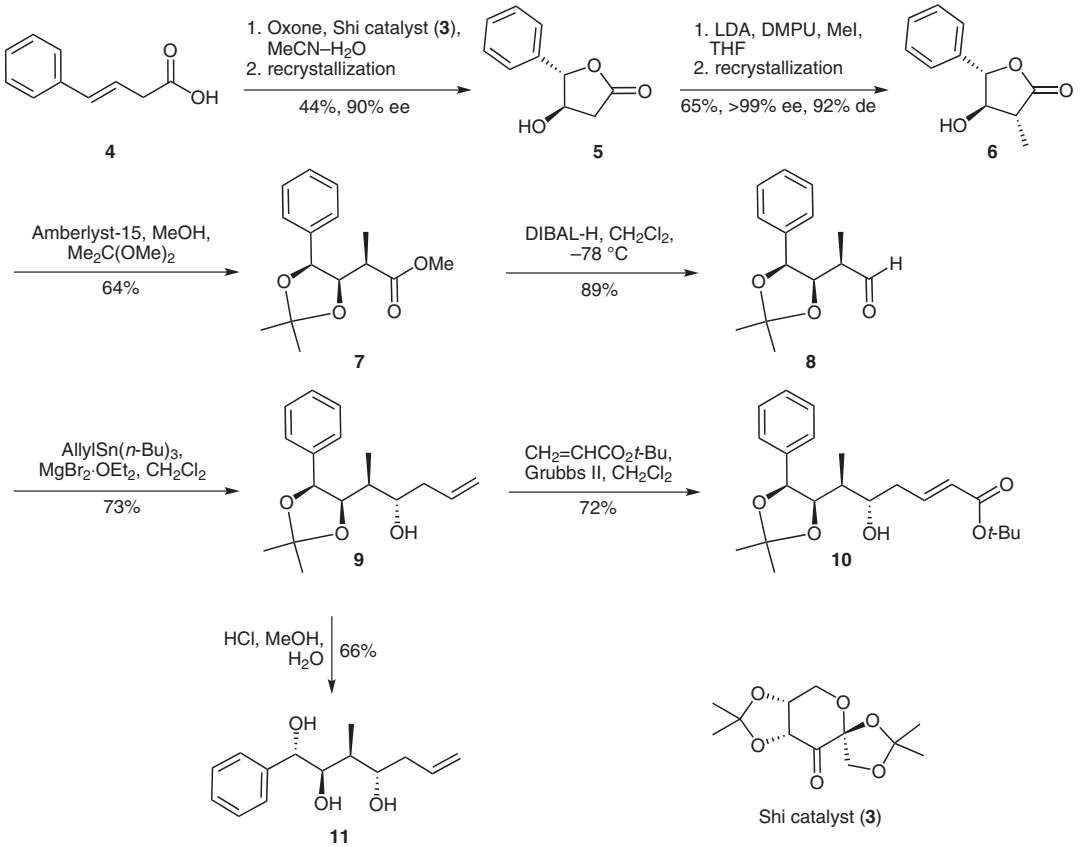
Hydroxy lactone **5** was chemoselectively methylated in the *anti*-position to the hydroxyl group using LDA/methyl iodide and DMPU.

The stereochemical purity of the crude α-methylated lactone **6** (90% ee, 85% de) was increased by recrystalliza-

Table 1 Asymmetric and Racemic Tandem Epoxidation and Lactonization Reaction of β,γ-Unsaturated Acids

Entry	Acid	Yield (%)	ee (%)
1	**4**	44 82 (rac.)	90[a] –
2		33 77 (rac.)	45 –
3		15 51 (rac.)	82 –
4		0 0 (rac.)	– –
5		0 0 (rac.)	– –

[a] After recrystallization.



Scheme 1 Synthesis of cryptophycin-39 unit A building blocks **9** and **10**

tion to more than 99% ee (determined by chiral HPLC) and 92% de in 65% yield. The addition of DMPU accelerated the reaction and the directing power of the hydroxy group sufficiently outweighed the detrimental influence of the phenyl substituent. While the absolute configuration in β- and γ-position of **5** was defined by the known enantioselectivity of the Shi epoxidation,[8,10] the X-ray crystal-structure analysis gave proof of the relative configuration of the methyl group in **6**. The observed ^{1}H NMR coupling constant (^3J = 9.5 Hz) between H^α and H^β in **6** was furthermore in accordance with published data for a similar system.[13]

Opening of lactone **6** by reaction with 2,2-dimethoxypropane, methanol, and Amberlyst-15[5,14] provided the methyl ester **7** with the sterically hindered *cis*-diol being concomitantly protected as an acetonide in 64% overall yield. Recovered starting material and intermediate products were subjected to the same reaction for a second time. Reduction of **7** with diisobutylaluminium hydride gave aldehyde **8** in 89% yield without any epimerization.

Diastereoselective allylation with allyltributylstannane under chelation by addition of $MgBr_2{\cdot}OEt_2$ was performed according to a protocol[15] published by Lee et al. and yielded homoallyl alcohol **9** in 73%. In fact, this compound is already a potential unit A precursor for an RCM approach.[5,16] A metathesis reaction with *tert*-butylacrylate gave rise to the more traditional unit A precursor **10** in 72% yield after six steps.[17] This six-step synthesis represents the shortest route to a cryptophycin unit A precursor with four stereogenic centers, so far.

To prove the diastereoselectivity of the allylation, homoallyl alcohol **9** was deprotected with aqueous hydrochloric acid in methanol in 66% yield to provide the crystalline triol **11**, which was subjected to X-ray crystal-structure analysis.[18]

In summary, a synthesis of the cryptophycin-39 unit A building blocks **9** and **10** was developed in five and six steps, respectively. Furthermore, it was shown that the Shi epoxidation can be used for the very efficient and straightforward synthesis of a versatile lactone, which served as key building block in an economical asymmetric synthesis.

Acknowledgment

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References and Notes

(1) (a) Schwartz, R. E.; Hirsch, C. F.; Sesin, D. F.; Flor, J. E.; Chartrain, M.; Fromtling, R. E.; Harris, G. H.; Salvatore, M. J.; Liesch, J. M.; Yudin, K. *J. Ind. Microbiol.* **1990**, *5*, 113. (b) Trimurtulu, G.; Ohtani, I.; Patterson, G. M. L.; Moore, R. E.; Corbett, T. H.; Valeriote, F. A.; Demchik, L. *J. Am. Chem. Soc.* **1994**, *116*, 4729. (c) Golakoti, T.; Ogino, J.; Heltzel, C. E.; Husebo, T. L.; Jensen, C. M.; Larsen, L. K.; Patterson, G. M. L.; Moore, R. E.; Mooberry, S. L.; Corbett, T. H.; Valeriote, F. A. *J. Am. Chem. Soc.* **1995**, *117*, 12030. (d) Kobayashi, M.; Kurosu, M.; Ohyabu, N.; Wang, W.; Fujii, S.; Kitagawa, I. *Chem. Pharm. Bull.* **1994**, *42*, 2196. (e) Kobayashi, M.; Aoki, S.; Ohyabu, N.; Kurosu, M.; Wang, W.; Kitagawa, I. *Tetrahedron Lett.* **1994**, *35*, 7969. For reviews, see: (f) Eißler, S.; Stončius, A.; Nahrwold, M.; Sewald, N. *Synthesis* **2006**, 3747. (g) Eggen, M.; Georg, G. I. *Med. Res. Rev.* **2002**, *22*, 85. (h) Tius, M. A. *Tetrahedron* **2002**, *58*, 4343.

(2) (a) Al-awar, R. S.; Corbett, T. H.; Ray, J. E.; Polin, L.; Kennedy, J. H.; Wagner, M. M.; Williams, D. C. *Mol. Cancer Ther.* **2004**, *9*, 1061. (b) Smith, C. D.; Zhang, X.; Mooberry, S. L.; Patterson, G. M.; Moore, R. E. *Cancer Res.* **1994**, *54*, 3779.

(3) Chaganty, S.; Golakoti, T.; Heltzel, C.; Moore, R. E.; Yoshida, W. Y. *J. Nat. Prod.* **2004**, *67*, 1403.

(4) (a) Gardinier, K. M.; Leahy, J. W. *J. Org. Chem.* **1997**, *62*, 7098. (b) Liang, J.; Moher, E. D.; Moore, R. E.; Hoard, D. W. *J. Org. Chem.* **2000**, *65*, 3143. (c) Pousset, C.; Haddad, M.; Larchevêque, M. *Tetrahedron* **2001**, *57*, 7163. (d) Li, L.-H.; Tius, M. A. *Org. Lett.* **2002**, *4*, 1637. (e) Mast, C. A.; Eißler, S.; Stončius, A.; Stammler, H.-G.; Neumann, B.; Sewald, N. *Chem. Eur. J.* **2005**, *11*, 4667.

(5) Eißler, S.; Nahrwold, M.; Neumann, B.; Stammler, H.-G.; Sewald, N. *Org. Lett.* **2007**, *9*, 817.

(6) Kino, R.; Daikai, K.; Kawanami, T.; Furuno, H.; Inanaga, J. *Org. Biomol. Chem.* **2004**, *2*, 1822.

(7) van Horn, J. D.; Burrows, C. J. *Tetrahedron Lett.* **1999**, *40*, 2069.

(8) (a) Wang, Z. X.; Tu, Y.; Frohn, M.; Zhang, J. R.; Shi, Y. *J. Am. Chem. Soc.* **1997**, *119*, 11224. (b) Wang, Z. X.; Tu, Y.; Frohn, M.; Shi, Y. *J. Org. Chem.* **1997**, *62*, 2328. (c) Shi, Y. *Acc. Chem. Res.* **2004**, *37*, 488. (d) Wong, O. A.; Shi, Y. *Chem. Rev.* **2008**, *108*, 3958.

(9) Hoard, D. W.; Moher, E. D.; Martinelli, M. J.; Norman, B. H. *Org. Lett.* **2002**, *4*, 1813.

(10) Ager, D. J.; Anderson, K.; Oblinger, E.; Shi, Y.; VanderRoest, J. *Org. Process Res. Dev.* **2007**, *11*, 44.

(11) **Synthesis of (4*R*,5*S*)-4-hydroxy-5-phenyl-tetrahydrofuran-2-one (5)**
trans-Styryl acetic acid (**4**, 21.8 mmol, 3.54 g) was dissolved in MeCN (210 mL). Aqueous KOH soln (1 M, 21.8 mmol, 21.8 mL), acetate buffer (150 mL, prepared by adding 5.00 mL AcOH to 13.82 g K_2CO_3 in 1000 mL H_2O and pH adjusted to 9.3 by the dropwise addition of concd aq NaOH soln) and *n*-Bu_4NHSO_4 (0.954 mmol, 324 mg) were added. The solution was cooled to 0 °C and Shi catalyst (**3**, 7.16 mmol, 1.85 g) was added. Freshly prepared Oxone (29.90 mmol, 18.36 g) in aq Na_2EDTA solution (0.4 mM, 0.0432 mmol, 108 mL) and aq K_2CO_3 soln (108 mL, prepared by dissolving 32.00 g K_2CO_3 in 200 mL H_2O) were separately added within 120 min at 0 °C. The cooling bath was removed, and the mixture was stirred for 180 min. Aqueous HCl (6 M, 0.36 mol, 60 mL) was carefully added. The solution was extracted with Et_2O (1 × 600 mL and 2 × 500 mL). The combined organic layers were washed with sat. aq $NaHCO_3$ solution (200 mL) and brine (30 mL). After drying over Na_2SO_4 the solvent was removed in vacuo (40 °C) and the crude material was purified by flash chromatography (hexane–EtOAc 3:2) giving a crystalline solid (10.78 mmol, 1.920 g, 82% ee), which was recrystallized from EtOAc (3.5 mL) at 2 °C overnight yielding (4*R*,5*S*)-4-hydroxy-5-phenyl-tetrahydrofuran-2-one (**5**, 9.58 mmol, 1.708 g, 44%, 90% ee) as a colorless solid; $[\alpha]_D^{24}$ 2.57 (*c* 1.38, $CHCl_3$). HPLC [Chiralpak AD, 2-PrOH–hexane (1:9), 1 mL/min]:

t_R = 16.6 min (**5**), 12.2 min (*ent*-**5**). Anal. Calcd (%) for $C_{10}H_{10}O_3$: C, 67.41; H, 5.66. Found: C, 67.39; H, 5.67. Further analytical data are in accordance with ref. 7.

(12) **General Procedure for the Synthesis of Substituted *trans*-Styryl Acetic Acids (Table 1, Entries 2 and 3)**
KO*t*-Bu (13 mmol, 1.469 g) in THF (14 mL) was added to a solution of the substituted benzaldehyde (9 mmol) and (2-carboxyethyl)triphenylphosphonium bromide (6 mmol, 2.494 g) in THF (12 mL) at 0 °C over 15 min. After stirring for additional 15 min at 0 °C and overnight at r.t., H_2O (10 mL) and Et_2O (50 mL) were added. The phases were acidified with 6 M aq HCl soln to pH 1 and separated. The aqueous phase was extracted with Et_2O (50 mL). The combined organic phases were extracted with sat. aq $NaHCO_3$ soln (2 × 60 mL). The sat. aq $NaHCO_3$ phases were washed with EtOAc (3 × 90 mL), acidified with concd aq HCl to pH 1 and extracted with Et_2O (2 × 75 mL). The organic extracts were washed with H_2O (20 mL) and brine (10 mL). After drying over Na_2SO_4 the solvent was removed in vacuo (40 °C) yielding the corresponding substituted *trans*-styryl acetic acid in 70–74% yield.

(13) (a) **Synthesis of (3*R*,4*R*,5*S*)-4-Hydroxy-3-methyl-5-phenyl-tetrahydrofuran-2-one (6)**
Diisopropylamine (11.56 mmol, 1.6 mL) in THF (28 mL) was cooled to –78 °C, then *n*-BuLi (1.6 M in hexane, 11.49 mmol, 7.2 mL) was added dropwise over 15 min. The solution was stirred for 15 min at –78 °C and for 30 min at r.t. The LDA solution was cooled to –78 °C again and DMPU (34.87 mmol, 4.2 mL) was added. After 45 min lactone (**5**, 4.60 mmol, 819 mg) in THF (19.2 mL) was added during 90 min. After stirring for 45 min and addition of THF (16 mL), MeI (46.6 mmol, 2.9 mL) in THF (8.6 mL) was added during 150 min. The solution was stirred overnight at –78 °C. Acetic acid (0.6 mL) in THF (1.0 mL) was added, and the suspension was warmed to r.t. Then, 5% aq Na_2SO_3 soln (8.8 mL) was added, and after 5 min the solvent was removed in vacuo (40 °C), until a pink suspension remained, which was partitioned between Et_2O (40 mL) and H_2O (20 mL). The aqueous layer was extracted with Et_2O (4 × 60 mL), and the combined organic phases were washed with 5% aq $KHSO_4$ soln (30 mL) and brine (15 mL). After drying over Na_2SO_4 the solvent was removed in vacuo (40 °C), and the residue was purified by flash chromatography (hexane–EtOAc, 7:3). The product (3.80 mmol, 731 mg, 90% ee, 85% de) was recrystallized in EtOAc (1 mL) at –22 °C overnight. A colorless solid (**6**, 3.00 mmol, 576 mg, 65%, >99% ee, 92% de) was obtained; $[\alpha]_D^{24}$ 6.21 (*c* 1.18, $CHCl_3$); mp 90 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.30–7.50 (m, 5 H), 5.06 (d, *J* = 7.5 Hz, 1 H), 3.98 (m, 1 H), 2.77 (dq, *J* = 9.4, 6.9 Hz, 1 H), 2.61 (d, *J* = 5.0 Hz, 1 H), 1.36 (d, *J* = 6.9 Hz, 3 H). ^{13}C NMR (126 MHz, $CDCl_3$): δ = 176.0, 136.6, 128.9, 128.8, 125.7, 84.2, 81.4, 43.6, 12.3. IR (neat): 3409, 3069, 3035, 2974, 2935, 2886, 1732, 1499, 1458, 1363, 1312, 1254, 1184, 1135, 1092, 971, 921, 854, 834, 765, 715, 695, 653 cm^{-1}. MS (EI): *m/z* = 192.1 [M$^+$], 174.1 [M$^+$ – H_2O], 107.0 [Ph – CHOH$^+$]. HRMS (EI): *m/z* calcd for $C_{11}H_{12}O_3^+$ [M$^+$]: 192.07864; found: 192.07934. HPLC [Chiralpak AD, 2-PrOH–hexane (1:9), 1 mL/min]: t_R = 13.4 min (**6**), 9.2 min (*ent*-**6**). Anal. Calcd (%) for $C_{11}H_{12}O_3$: C, 68.74; H, 6.29. Found: C, 68.67; H, 6.24. (b) Chen, S. Y.; Joullie, M. M. *J. Org. Chem.* **1984**, *49*, 2168. (c) CCDC 703492 contains the crystallographic data of **6**. They can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

(14) Harcken, C.; Brückner, R. *Synlett* **2001**, 718.

(15) Lee, E.; Jeong, E. J.; Kang, E. J.; Sung, L. T.; Hong, S. K. *J. Am. Chem. Soc.* **2001**, *123*, 10131.

(16) Tripathy, N. K.; Georg, G. I. *Tetrahedron Lett.* **2004**, *45*, 5309.

(17) **Synthesis of (5*S*,6*S*,*E*)-*tert*-Butyl-6-[(4*R*,5*S*)-2,2-dimethyl-5-phenyl-1,3-dioxolan-4-yl]-5-hydroxyhept-2-enoate (10)**
Homoallyl alcohol **9** (0.615 mmol, 170 mg) in CH_2Cl_2 (0.85 mL) was added to a solution of Grubbs II catalyst (0.026 mmol, 22.1 mg) and *tert*-butylacrylate (0.513 mmol, 74.4 μL) in CH_2Cl_2 (3.4 mL). The solution was refluxed in the dark overnight. The solvent was removed in vacuo (30 °C), and the residue was purified by flash chromatography (hexane–EtOAc, 8:2) yielding **10** (0.369 mmol, 138.8 mg, 72%) as a colorless oil; $[\alpha]_D^{24}$ –7.50 (*c* 1.10, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.28–7.40 (m, 5 H), 6.77 (m, 1 H), 5.80 (d, *J* = 15.7 Hz, 1 H), 5.38 (d, *J* = 7.5 Hz, 1 H), 4.70 (dd, *J* = 3.8, 7.5 Hz, 1 H), 3.50 (m, 1 H), 2.37 (m, 1 H), 2.22 (m, 1 H), 1.58–1.72 (m, 4 H), 1.41–1.56 (m, 12 H), 0.71 (d, *J* = 6.9 Hz, 3 H). ^{13}C NMR (126 MHz, $CDCl_3$): δ = 165.5, 144.0, 138.0, 128.2, 127.5, 126.6 125.7, 108.2, 80.3, 79.4, 78.1, 73.5, 38.3, 37.4, 28.2, 26.3 24.7, 11.2. IR (neat): 3453, 2979, 2934, 2360, 1709, 1651, 1494, 1454, 1379, 1367, 1326, 1253, 1210, 1086, 1044, 1029, 1006, 980, 917, 879, 850, 730, 700, 647, 512, 466 cm^{-1}. ESI-MS: *m/z* = 399.2 [M + Na$^+$]. ESI-HRMS: *m/z* calcd for $C_{22}H_{32}O_5Na^+$ [M + Na$^+$]: 399.21420; found: 399.21373.

(18) (a) **Synthesis of (1*S*,2*R*,3*S*,4*S*)-3-Methyl-1-phenylhept-6-ene-1,2,4-triol (11)**
A 5% aq HCl soln (4 mL) was added to a solution of homoallyl alcohol **9** (0.615 mmol, 170.0 mg) in MeOH (6 mL). After refluxing the solution for 90 min MeOH was removed in vacuo (40 °C), and the aqueous phase was extracted with Et_2O (5 × 30 mL), dried over $MgSO_4$, and purified by flash chromatography (hexane–EtOAc, 7:3). A colorless crystalline solid (**11**, 0.405 mmol, 95.7 mg, 66%) was obtained; $[\alpha]_D^{24}$ 43.59 (*c* 1.22, $CHCl_3$); mp 77 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.26–7.49 (m, 5 H), 5.80 (m, 1 H), 5.13–5.20 (m, 2 H), 4.70 (δ, *J* = 7.5 Hz, 1 H), 4.15 (d, *J* = 7.5 Hz, 1 H), 3.70 (m, 1 H), 2.60 (d, *J* = 2.5 Hz, 1 H), 2.27–2.44 (m, 3 H), 2.21 (s, 1 H), 1.98 (m, 1 H), 1.16 (d, *J* = 6.9 Hz, 3 H). ^{13}C NMR (126 MHz, $CDCl_3$): δ = 141.8, 134.8, 128.6, 128.1, 126.8, 118.4, 75.1 75.0, 74.1, 40.0, 37.2, 11.2. IR (neat): 3545, 3345, 3063, 3030, 2970, 2923, 2360, 2341, 1639, 1493, 1455, 1431, 1404, 1382, 1340, 1269, 1212, 1135, 1071, 1023, 1000, 989, 974, 917, 870, 842, 786, 697, 639, 604, 544, 475, 419 cm^{-1}. ESI-MS: *m/z* = 259.2 [M + Na$^+$]. ESI-HRMS: *m/z* calcd for $C_{14}H_{20}O_3Na^+$ [M + Na$^+$] 259.13047; found: 259.13030. Anal. Calcd (%) for $C_{14}H_{20}O_3$: C, 71.16; H, 8.53. Found: C, 71.00; H, 8.60.
(b) CCDC 703493 contains the crystallographic data of **11**. They can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.