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Efficient synthesis of a 4,5-epoxy-2-cyclohexen-1-one derivative bearing a spirolactone *via* a Diels–Alder reaction with high π-facial selectivity: a synthetic study towards scyphostatin

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The Diels–Alder reaction of spirolactones with cyclopentadiene afforded the adduct with high π-facial selectivity; a hydrophilic analogue of scyphostatin was synthesized from the Diels–Alder adduct.

Scyphostatin **1** (Fig. 1) was isolated from the mycelial extract of *Dasyscyphus mollissima* by Ogita and coworkers (Sankyo Co Ltd., Japan) in 1997 and was found to be a potent inhibitor of neutral sphingomyerinase (N-SMase).[1] Scyphostatin **1** consists of a hydrophobic side chain and a hydrophilic 4,5-epoxy-2-cyclohexen-1-one moiety. Our interest in such biphilic natural products[2] has inspired us to carry out synthetic studies on scyphostatin **1**. Other groups have also reported synthetic efforts.[3] In this paper, the efficient synthesis of hydrophilic analogue **2** *via* a Diels–Alder reaction with high π-facial selectivity is described.

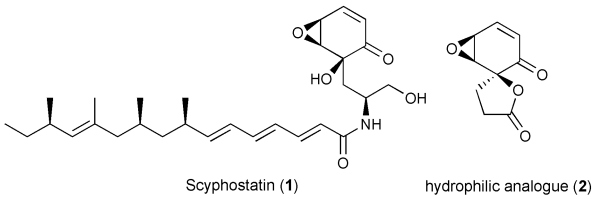
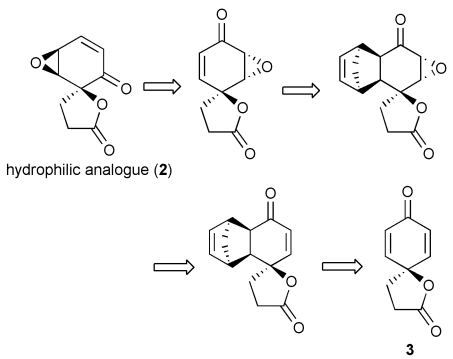


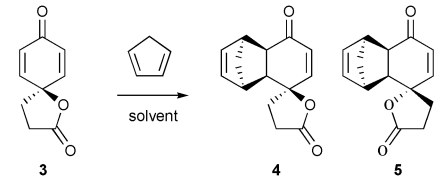
Fig. 1

Masked benzoquinones, obtained by the Diels–Alder reaction of cyclopentadiene and *p*-benzoquinones, have proven useful as precursors to highly functionalized cyclohexane derivatives.[4] Especially notewortly is the high π-facial selectivity in the Diels–Alder reaction of spirolactone **3** with sterically hindered chiral bicyclic cyclopentadiene derivatives reported by Winterfeldt *et al.*[5] Thus, we decided to look into the possibility using of this strategy by reacting spirolactone with sterically undemanding cyclopentadienes for the preparation of the hydrophilic moiety as outlined in Scheme 1.

The spirolactone **3** was synthesized by oxidative intramolecular lactonization with $PhI(OAc)_2$.[6] The Diels–Alder reaction of spirolactone **3** with cyclopentadiene in CH_2Cl_2 and CF_3CH_2OH preferentially afforded the adduct **4** (**4**:**5** = 96:4,



Scheme 1



solvent	conditions	4 : 5	yields (%)
CH_2Cl_2	25 °C, 3 days	96 : 4	99
CH_3CN	35 °C, 3 days	91 : 9	72
CF_3CH_2OH	37 °C, 4 h	96 : 4	87

Scheme 2

Scheme 2). The Diels–Alder reaction of spirolactone **3** was accelerated in CF_3CH_2OH. When CH_3CN was used as a solvent, the π-facial selectivity of spirolactone **3** with cyclopentadiene slightly decreased (**4**:**5** = 91:9). The mixtures of the adducts could be separated by HPLC. The stereochemistry of the adducts **4** and **5** was assigned by ^1H NMR NOE experiments (Fig. 2).[7] Thus, we have found that even if the diene is sterically undemanding, the Diels–Alder reaction of spirolactone **3** proceeds with high π-facial selectivity.

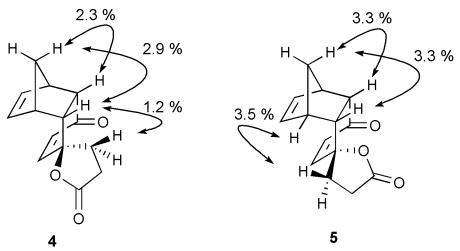
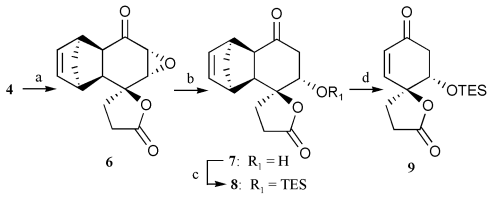


Fig. 2 Determination of the relative stereochemistry of adducts **4** and **5**.

The high π-facial selectivity in Diels–Alder reaction of spirolactone **3** with cyclopentadiene prompted us to use it for the synthesis of **2**, a model compound for the hydrophilic moiety of scyphostatin **1** (Scheme 3). Epoxide **6** was obtained by epoxidation with H_2O_2/LiOH, followed by reclosure to the lactone ring with 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide (WSCI) (66% over two steps). The epoxide ring of **6** was reductively cleavaged with SmI_2 (89%) to give **7** as the only ring opened product.[8] Protection of the secondary alcohol with



Scheme 3 *Reagents and conditions*: (a) 30% H_2O_2, LiOH, THF, 0 °C, then WSCI, CH_2Cl_2, 25 °C, 66% over two steps; (b) SmI_2, MeOH, THF, −78 °C, 89%; (c) TESCl, imidazole, CH_2Cl_2, 25 °C, 100%; (d) maleic anhydride, Ph_2O, 230 °C, 96%.

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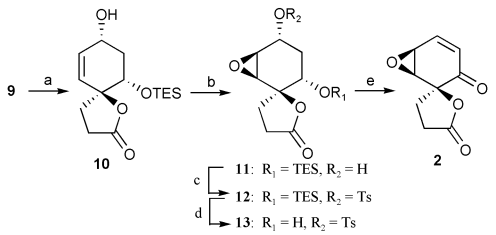
triethyl silyl group (TES) gave **8** (100%). Retro-Diels–Alder product **9** was obtained by heating (230 °C) **8** in the presence of maleic anhydride (96%).

With 5-hydroxy-2-cyclohexen-1-one bearing a spirolactone **9** in hand, we focused our attention on its conversion to 4,5-epoxy-2-cyclohexen-1-one (Scheme 4). Treatment of **9** with $NaBH_4/CeCl_3$ gave alcohol **10** as a single isomer (99%). The relative stereochemistry was assigned by coupling constants ($J_{H1–H2ax}$, $J_{H2ax–H3}$) and NOE experiments in ^{1}H NMR (Fig. 3). Contrary to our expectations, epoxide **11** was obtained as a singal isomer upon epoxidation of **10** with 3-chloroperoxybenzoic acid (*m*CPBA) (95%).[9] The relative stereochemistry was determined by ^{1}H NMR NOE experiments and coupling constants (Fig. 3). NOE enhancement between H5 and H7 was observed. The observed facial selectivity in the epoxidation reaction can be attributed to attack on the face opposite to the lactone CH_2 group to avoid repulsion, despite the presence of a hydroxy directing group (Fig. 4). Epoxide **11** was converted to epoxide **13** by tosylation, followed by removal of the TES group with TBAF (59% over two steps). When epoxide **13** was treated under Swern oxidation conditions, 4,5-epoxy-2-cyclohexen-1-one, bearing a spirolactone **2**, a hydrophilic analogue of scyphostatin **1**, was obtained with simultaneous extrusion of the TsO group (75%).[10]

In summary, we have developed a short and high efficient method of synthesizing of 4,5-epoxy-2-cyclohexen-1-one derivative **2**, a hydrophilic analogue of scyphostatin **1**. The method features a highly selective Diels–Alder reaction, reductive oxirane ring opening, 1,2-enone reduction, and subsequent epoxidation. Investigations towards the total synthesis of scyphostatin **1** based on this convenient strategy is now in progress.



Scheme 4 *Reagents and conditions*: (a) $NaBH_4$, $CeCl_3{\cdot}7H_2O$, THF, *i*PrOH, 0 °C, 99%; (b) *m*CPBA, CH_2Cl_2, 25 °C, 95%; (c) TsCl, DABCO, CH_2Cl_2, 25 °C, 79%; (d) TBAF, AcOH, THF, 25 °C, 75%; (e) $(COCl)_2$, DMSO, CH_2Cl_2, −60 °C, 75%.

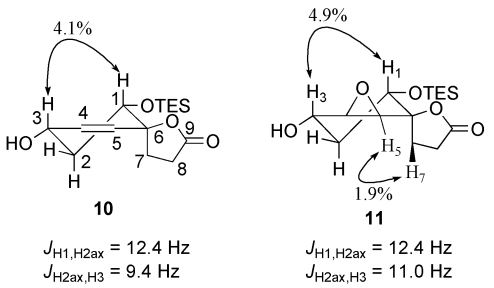


Fig. 3 Determination of the relative stereochemistry of **10** and **11**.

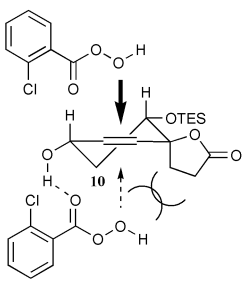


Fig. 4 Stereoselectivity in epoxidation of **10** with *m*CPBA.

The measurements of NMR and MS were made using JEOL JMN-LA500 and JEOL SX-102A, respectively, at the Instrument Center for Chemical Analysis, Hiroshima University. We thank Dr. Yoshikazu Hiraga for measurements of NMR (JEOL JMN-LA500) at the Hiroshima Prefectural Institute of Science and Technology. Financial supports of this work through Grant-in-Aid for Scientific Research (no.11740355 and no.14740349) provided by the Japan Society for the Promotion of Science and KANEKO-NARITA Research Bounty by Protein Research Foundation are heartily acknowledged. The authors thank F-TECH, Inc. for the gift of CF_3CH_2OH.

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7 *Spectral data*: **4**: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.35 (d, 1 H, *J* 8.7 Hz), 1.48 (d, 1 H, *J* 8.7 Hz), 2.15–2.27 (m, 2 H), 2.62 (ddd, 1 H, *J* 3.7, 8.5, 17.9 Hz), 2.78 (ddd, 1 H, *J* 9.2, 10.8, 17.9 Hz), 2.88 (ddd, 1 H, *J* 1.2, 3.3, 8.7 Hz), 3.04 (dd, 1 H, *J* 4.4, 8.7 Hz), 3.18 (m, 1 H), 3.39 (m, 1 H), 5.85 (dd, 1 H, *J* 1.1, 9.2 Hz), 5.87 (dd, 1 H, *J* 1.1, 10.0 Hz), 6.14 (dd, 1 H, *J* 2.5, 10.0 Hz), 6.52 (dd, 1 H, *J* 2.5, 9.2 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 27.5, 38.6, 45.2, 47.5, 47.4, 48.7, 50.8, 83.0, 130.7, 134.8, 135.4, 148.9, 175.9, 199.1; EI-HRMS *m*/*z* 230.0940 (M^+, $C_{14}H_{14}O_3$ requires 230.0943). **5**: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.47 (d, 1 H, *J* 8.6), 1.57 (dt, 1 H, *J* 1.6, 8.6 Hz), 2.17 (ddd, 1 H, *J* 4.6, 15.4, 13.1 Hz), 2.60 (ddd, 1 H, *J* 9.0, 10.4, 13.1 Hz), 2.71-2.78 (m, 2 H), 3.02 (ddd, 1 H, *J* 1.3, 3.2, 8.4 Hz), 3.19 (dd, 1 H, *J* 4.4, 8.4 Hz), 3.24 (s, 1 H), 3.44 (s, 1 H), 5.96-6.01 (m, 2 H), 6.07 (d, 1 H, *J* 10.2 Hz), 6.45 (dd, 1 H, *J* 1.3, 10.2 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 28.55, 31.88, 46.37, 46.47, 47.01, 49.38, 49.87, 82.23, 132.92, 134.10, 136.18, 143.02, 174.84, 199.11; FAB-HRMS *m*/*z* 231.1015 (M + H, $C_{14}H_{15}O_3$ requires 231.1021).

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10 *Spectral data* for **2**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.38 (dt, 1 H, *J* 9.1, 13.2 Hz), 2.70 (ddd, 1 H, *J* 3.8, 9.1, 17.5 Hz), 2.78 (ddd, 1 H, *J* 3.8, 9.2, 13.2 Hz), 2.94 (ddd, 1 H, *J* 9.1, 9.2, 17.5 Hz), 3.64 (dd, 1 H, *J* 3.4, 4.0 Hz), 3.79 (d, 1 H, *J* 3.4 Hz), 6.20 (d, 1 H, *J* 10.2 Hz), 7.26 (dd, 1 H, *J* 4.0, 10.2 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 28.1, 28.2, 47.3, 58.7, 80.1, 130.8, 145.0, 175.6, 191.1; EI-HRMS *m*/*z* 180.0430 (M^+, $C_9H_8O_4$ requires 180.0423).