Total Synthesis of Prelaureatin

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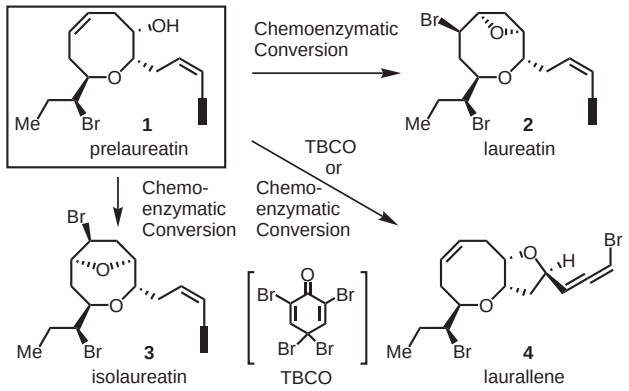
Abstract: Total synthesis of prelaureatin, which is an 8-membered cyclic ether isolated from red alga *Laurencia nipponica*, has been achieved through a process including stereoselective introduction of two allyl groups starting from galactose pentaacetate, cleavage of the hexose ring, and transformation of an acyclic triene into an oxocene by selective ring-closing metathesis.

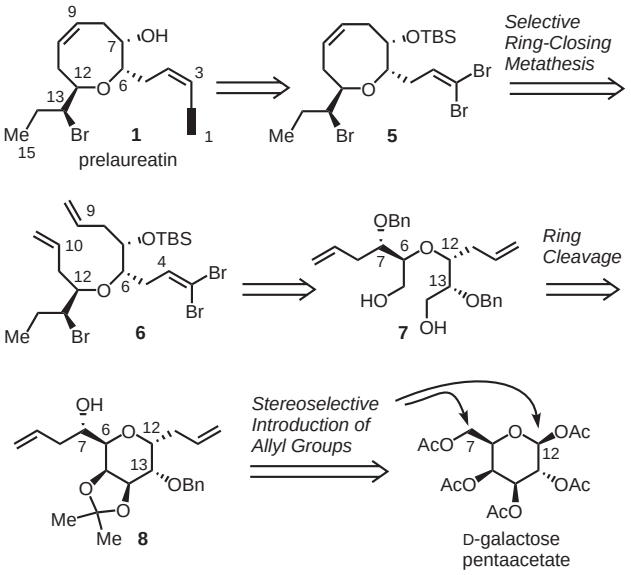
Key words: total synthesis, stereoselective synthesis, natural products, ethers, metathesis

Prelaureatin **1**[1] has been isolated from red alga *Laurencia nipponica* as an 8-membered cyclic ether which belongs to laurenan family of C15-acetogenins involving laureatin **2**,[2] isolaureatin **3**,[2] and laurallene **4**.[3] Laurenans show interest bioactivities, such as potent insecticidal activities of **2** and **3** as well as anticonvulsant activity of **3**.[4,5] Our previous chemoenzymatic studies using bromoperoxidase from *Laurencia nipponica* or lactoperoxidase have demonstrated that **1** is a key precursor in the biosynthetic route to laurenans **2**, **3**, and **4** (Scheme 1).[6] These results have also shown a possibility of the chemical syntheses of all these laurenans from **1**. In fact, this possibility has partly been proved by the production of **4** after the reaction of **1** with 2,4,4,6-tetrabromo-2,5-cyclohexadien-1-one (TBCO).[6b] Thus, we planned total synthesis of **1**,[7] an important synthetic intermediate for other laurenan compounds.

Our synthetic strategy is shown in Scheme 2. We planned to synthesize **1** from triene **6** through a sequence of selective ring-closing olefin metathesis (RCM) reaction[8,9] of **6** and construction of *Z*-enyne part of the resulting **5** by Uenishi's protocol.[10] We expected that triene **6**, which has three combinations of reactive sites [C4–C9 (forming a cyclohexene), C4–C10 (forming an oxepene), and C9–C10 (forming an oxocene)], would prefer a reaction between less-hindered olefins rather than formation of a smaller-sized ring in RCM conditions.[11] Further, this strategy would also rely on the successful preparation of precursor **6**. Since asymmetric synthesis of chiral secondary dialkyl ether is not so facile, efficient construction of asymmetric centers at C6 and C12 is an important challenge in total synthesis of **1**. We adopted C-glycoside **8** as a key synthetic intermediate having the desired stereochemistries at C6, C7, C12, and C13, which would be derived from D-galactose pentaacetate through a process of stereoselective introduction of allyl groups at C7 and C12 (corresponding to C1 and C6 in the position numbering of glycoside, respectively). Cleavage of the hexose ring in **8** followed by conversion of the side chains in the resulting **7** would provide **6**.



Scheme 1



Scheme 2

Our actual synthesis of **1** is shown in Scheme 3. Allylation of D-glucose pentaacetate was performed with allyltrimethylsilane in the presence of $BF_3{\cdot}OEt_3$ according to Gian-

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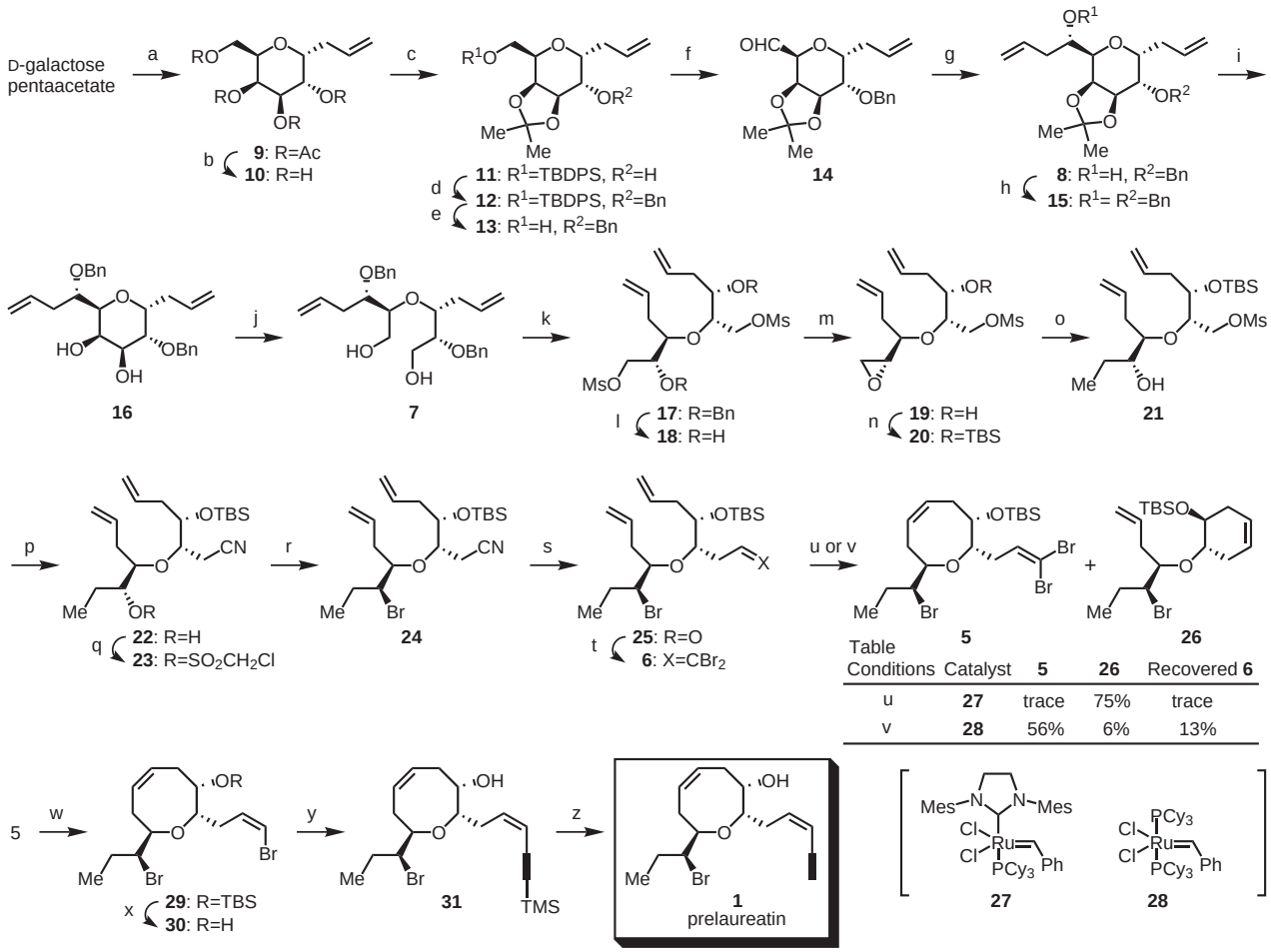
nis' method[12] to give **9** selectively in 83% yield, which was converted to **13** in 80% total yield through a 4-step process [(i) deacetylation, (ii) one-pot protection of a primary hydroxyl group with TBDPSCl and a *cis*-diol part with dimethoxypropane, (iii) protection with BnBr, and (iv) desilylation]. Swern oxidation[13] of **13** followed by treatment with allyltributyltin under Grieco's conditions[14] afforded **8** stereoselectively in 79% yield along with 5% production of the diastereomer of **8**.

Alcohol **8** was protected with BnBr and the resulting **15** was deprotected to produce diol **16** in 94% overall yield, which was converted to diol **7** in 99% yield by a sequence of oxidative cleavage and reduction. Mesylation of the diol followed by removal of benzyl groups gave **18**, which was treated with K_2CO_3 to afford epoxide **19** in 83% total yield. Protection of the hydroxy group of **19** with TBSCl and the subsequent ring opening of the epoxide with Me_2CuLi produced **21** in 81% overall yield. Cyanation of **21** with Bu_4NCN at 50 °C gave **22** in 78% yield together with 22% recovery of **21**. When the reaction was performed at higher temperature, significant decomposition of **22** competed. Bromide **24** was synthesized from **22** in 82% total yield via a stepwise route [(i) transformation into monochloromethanesulfonate ester[15] **23** and (ii) treatment of **23** with LiBr in THF], because direct bromination of **22** with Oct_3P-CBr_4[16] or DPPE-$2Br_2$[17] only led to decomposition. Nitrile **24** was reduced with DIBALH and



Scheme 3 Reagents and conditions: (a) allyltrimethylsilane, $BF_3{\cdot}OEt_2$, MeCN, 5 °C, 95 h, 83%; (b) MeONa, MeOH, 0 °C, 48 h, 89%; (c) TBDPSCl, imidazole, DMF, 24 °C, 30 min, then CSA, $(MeO)_2CMe_2$, 24 °C, 1.5 h, 91%; (d) NaH, BnBr, Bu_4NI, THF, 24 °C, 30 h, 99%; (e) TBAF, THF, 23 °C, 2 h, ~100%; (f) $(COCl)_2$, DMSO, CH_2Cl_2, –78 °C, 20 min, then Et_3N, –78 °C → 0 °C, 5 min; (g) allyltributyltin, 2.3 M $LiClO_4$ in Et_2O, 23 °C, 23 h, **8**: 79% from **13**, diastereomer of **8**: 5% from **13**; (h) NaH, BnBr, Bu_4NI, THF, 25 °C, 22 h, ~100%; (i) 12 M aq HCl–THF (1:5.3), 23 °C, 3.5 h, 94%; (j) $NaIO_4$, MeOH–pH 7 buffer (3:1), 23 °C, 1.3 h; $NaBH_4$, MeOH, 0 °C → 23 °C, 2 h, 99% from **16**; (k) MsCl, Et_3N, CH_2Cl_2, 0 °C → 25 °C, 3.5 h, ~100%; (l) DDQ, 1,2-dichloroethane–H_2O (9:1), reflux, 26 h; (m) K_2CO_3, MeOH, 25 °C, 50 min, 83% from **17**; (n) TBSOTf, 2,6-lutidine, CH_2Cl_2, 23 °C, 4 h, 98%; (o) MeLi, CuI, THF, –20 °C, 1 h, 83%; (p) Bu_4NCN (excess), DMSO, 50 °C, 4.5 h, **22**: 78%, **21**: 22% recovery; (q) $ClCH_2SO_2Cl$, 2,6-lutidine, CH_2Cl_2, 0 °C, 20 min; (r) 0.7 M LiBr in THF, 25 °C, 47 h, 82% from **22**; (s) DIBAL, CH_2Cl_2, –78 °C, 15 min; (t) CBr_4, Ph_3P, CH_2Cl_2, 0 °C → 23 °C, 90 min, **6**: 44% from **24**, **24**: 43% recovery; (u) **27** (0.66 equiv), CH_2Cl_2 (2 mM of **6**), 35 °C, 32 h, **26**: 75%; (v) **28** (0.38 equiv), CH_2Cl_2 (2 mM of **6**), 35 °C, 37 h, **5**: 56%, **26**: 6%, **6**: 13% recovery; (w) $(Ph_3P)_4Pd$ (0.1 equiv), Bu_3SnH (13 equiv), Ph_3P (0.6 equiv), CH_2Cl_2, 25 °C, 6 h, 82%; (x) TFA–THF–H_2O (4:5:5), 22 °C, 5 h, 82%; (y) $(Ph_3P)_4Pd$ (0.15 equiv), CuI (1.4 equiv), ethynyltrimethylsilane (11 equiv), *i*-Pr_2NH (9 equiv), THF, 25 °C, 12 h, **31**: 46%, **30**: 52% recovery; (z) TBAF, THF–H_2O (55:1), 0 °C, 5 h, ~100%.

the resulting aldehyde **25** was subjected to Wittig reaction to afford **6** in 44% total yield with 43% recovery of **24**.

RCM reactions of **6** using two Grubbs' catalysts **27**[18] and **28**[19] gave the interesting results (Table in Scheme 3). While the use of catalyst **27** afforded cyclohexene **26** exclusively (75%), less-reactive catalyst **28** led to production of the desired oxocene **5** (56%, with 13% recovery of **6**) rather than **26** (6%) under the same conditions. In both cases, no oxepane product was observed.

Finally, the enyne part of **1** was constructed by a modification of Uenishi's protocol.[10] Selective hydrogenolysis of dibromoalkene part of **5** led to a formation of **29** in 82% yield. Although bromide **29** was inactive to Sonogashira coupling reaction[20] with ethynyltrimethylsilane, desilylated **30** could be coupled as expected under the same conditions to produce **31** in 46% yield with 52% recovery of **30**. Removal of TMS with TBAF in wet THF produced **1** in quantitative yield.[1,6b] Spectral data of synthetic **1** were identical with those of natural prelaureatin.[1] Thus, total synthesis of **1** was achieved in 26 steps from galactose pentaacetate.

In conclusion, total synthesis of prelaureatin, isolated from red alga *Laurencia nipponica*, has been achieved through a process including stereoselective introduction of two allyl groups starting from galactose pentaacetate, cleavage of the hexose ring, and transformation of an acyclic triene into an oxocene by selective ring-closing metathesis.

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