Natural Products Synthesis

Total Synthesis of (−)-Laulimalide: Pd-Catalyzed Stereospecific Ring Construction of the Substituted 3,6-Dihydro[2*H*]pyran Units**

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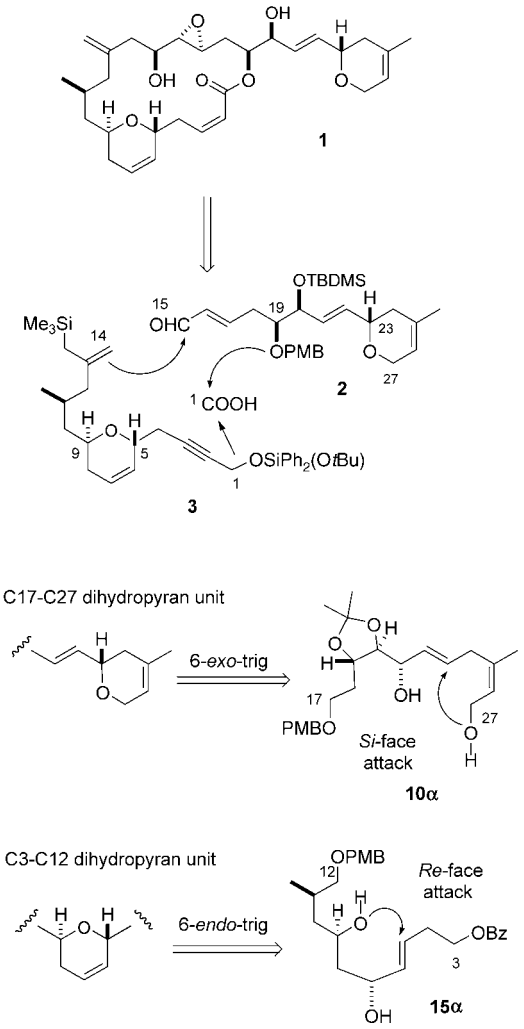
Laulimalide (**1**; Scheme 1) is a novel cancer-therapy agent isolated from the marine sponges *Hyattella* sp. and *Cacospongia mycofijiensis*.[1] Initially, **1** received considerable attention for its potent microtubulin-stabilizing profile, similar to that of taxol with a potency against multidrug-resistant cells at nanomolar concentrations.[2] Recently **1** received additional attention because it seems to have a binding site distinct from that of taxol at the tubulin polymers,[3a–c] which opens up the possibility of using it together with taxol as an enhanced treatment. Owing to its restricted natural supply and unique 18-membered structure, **1** has attracted the interest of synthetic organic chemists.[4] However, although several elegant total syntheses have been reported,[5] a more efficient and flexible synthesis is still required to provide further derivatives for biological evaluation. In particular, the 3,6-dihydro[2*H*]pyran unit is important not only in the synthesis of **1**, but also as a principal component in many biologically important marine natural products. Although these two 3,6-dihydro[2*H*]pyran rings of **1** have been elegantly constructed by olefin metathesis,[5a,c,e–h] hetero-Diels–Alder reaction,[5b,d,f,g] and a few other protocols,[5b,g] we sought a new and general synthetic method for the ring other than the previous methods, thus prompting us to investigate the synthesis of **1**.

Herein, we describe the total synthesis of **1** as well as a new preparation of the 3,6-dihydro[2*H*]pyran moiety based on Pd-catalyzed stereospecific ring formation. As illustrated in Scheme 1, the key reaction steps for our total synthesis of **1** involve the assembly of the two fragments **2** and **3** by Sakurai–Hosomi coupling and Yamaguchi macrolactonization as well as the stereospecific synthesis of two dihydropyran ring units by 6-*exo*-trig and 6-*endo*-trig cyclizations.



Scheme 1. Retrosynthetic analysis of (−)-laulimalide (**1**). TBDMS = *tert*-butyldimethylsilyl; PMB = *p*-methoxybenzyl; Bz = benzoyl.

The C17–C27 framework was readily prepared by Horner–Wadsworth–Emmons reaction of **4** with **5**, and successive diastereoselective reduction by $NaBH_4$ in the presence of $CeCl_3$ heptahydrate gave β-alcohol **6** in 56% yield in two steps (Scheme 2).[6] Mitsunobu reaction of **6** with benzoic acid gave a mixture of C21 and C23 α-benzoates **7α** and **7α′** in 81% yield as a 1:1 mixture with inversion of the configuration by S_N2 and S_N2' reactions. After cleavage of the TBDPS group with TBAF (nBu$_4$NF), the mixture of regioisomers was subjected to Pd^0-catalyzed intramolecular O-allylation with $[Pd_2(dba)_3]$ in the presence of neocuproine to furnish the desired (*S*)-**8** in 50% yield along with unconverted C21 benzoate **7α** in 44% yield.[7]

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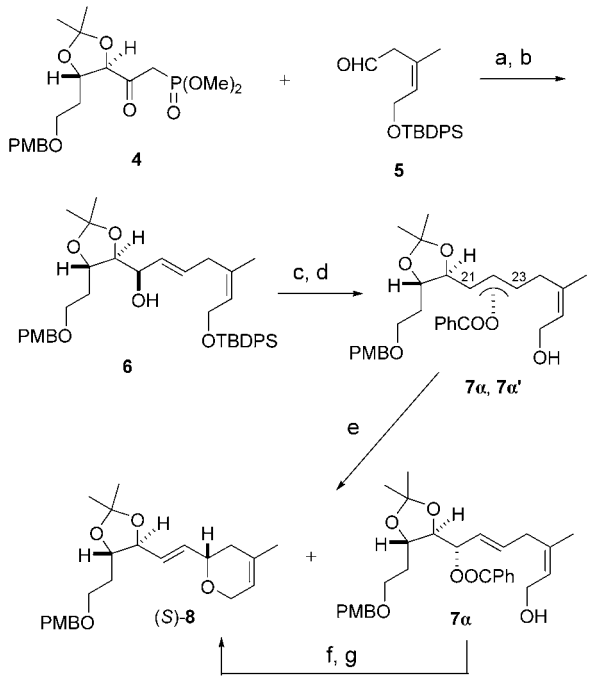
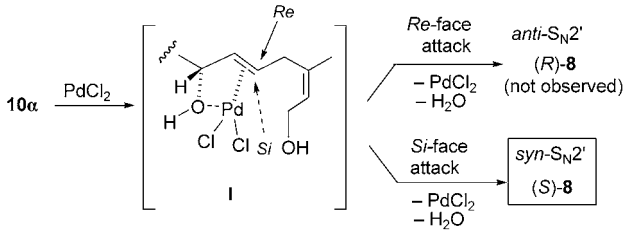


Scheme 2. Preparation of the C17–C27 unit. Reagents and conditions: a) K_2CO_3 THF/H_2O (1:1), room temperature, 70%; b) $NaBH_4$, $CeCl_3 \cdot 7H_2O$, MeOH, −78 °C→RT, 80%; c) DEAD, Ph_3P, PhCOOH, benzene, room temperature, 81%; d) TBAF, THF, room temperature, 86%; e) $[Pd_2(dba)_3]$ (20 mol%), neocuproine, toluene, room temperature, 89% (based on recovered **7α**); f) K_2CO_3, MeOH, room temperature, 97%; g) $[PdCl_2(CH_3CN)_2]$ (10 mol%), THF, 0 °C, 89%. DEAD = diethyl azodicarboxylate; TBAF = tetra-*n*-butylammonium fluoride; TBDPS = *tert*-butyldiphenylsilyl.

The results for the related Pd^0- and Pd^{II}-catalyzed ring formation of the C21 carbonates **9** and alcohols **10** are listed in Table 1. The reaction of **9α** and **9β** with $[Pd_2(dba)_3]$ proceeded stereospecifically to give the *syn*-S_N2'-reaction-type products (*S*)-**8** and (*R*)-**8** in 59% and 43% yield, respectively, by the net retention mechanism.[8] The reaction of **10α** with $[PdCl_2(CH_3CN)_2]$ gave the desired pyran (*S*)-**8** exclusively in 89% yield.[9] On the other hand, the β-diastereomer **10β** gave (*R*)-**8** stereospecifically in 77% yield.

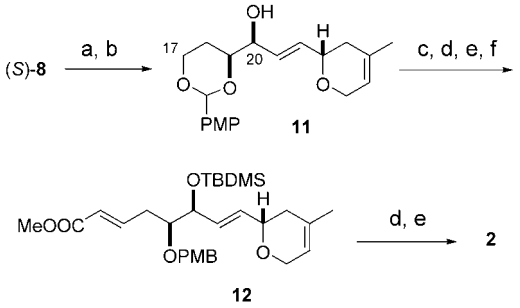
The 1,3 chirality transfer took place with retention of the configuration by an internal *syn*-S_N2'-type attack of the oxygen nucleophile in an *exo*-trig fashion (Scheme 3). When a Pd π-complex **I** is formed selectively on the same side of the double bond as the hydroxy group, the oxygen nucleophile attacks the olefinic carbon center from the *Si* face by a *syn*



Scheme 3. Synthesis of (*S*)-**8** by *syn*-S_N2' reaction of **10α**.

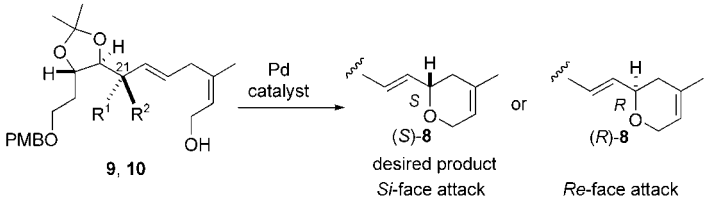
addition and successive *syn* elimination of Pd(OH)Cl from the resultant Pd σ-complex to give (*S*)-**8**.[10] In contrast, when the oxygen nucleophile attacks the olefinic carbon center of **I** from the *Re* face by an *anti* addition, the diastereomer (*R*)-**8** is obtained.[11]

After cleavage of the acetonide of (*S*)-**8**, oxidation of the diol with DDQ gave *p*-methoxybenzylidene acetal **11** in 77% yield over the two steps (Scheme 4). Subsequently, silylation



Scheme 4. Synthesis of **2**. Reagents and conditions: a) HCl, MeOH, room temperature, 89%; b) DDQ, molecular sieves (4 Å), CH_2Cl_2, 0 °C, 87%; c) TBDMSCl, imidazole, DMF, room temperature, 90%; d) DIBAL-H, CH_2Cl_2, −78 °C, 83%; e) DMP, 96%; f) $Ph_3PCHCOOMe$, benzene, room temperature, 92%; **12**→**2**: d) 98%; e) 94%. DDQ = 2,3-dichloro-5,6-dicyano-1,4-benzoquinone; DMF = *N*,*N*-dimethylformamide; DIBAL-H = diisobutylaluminum hydride; DMP = Dess–Martin periodinane.

Table 1: Pd^0- and Pd^{II}-catalyzed synthesis of (*S*)-**8** and (*R*)-**8**.

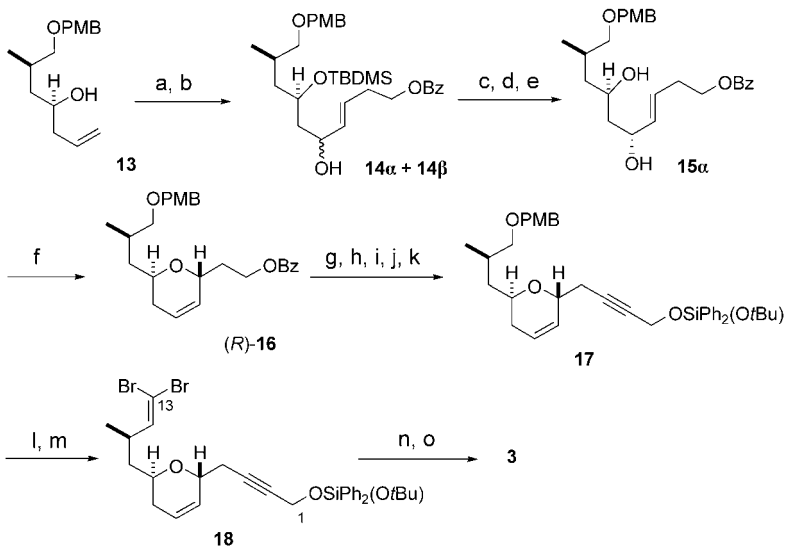


Entry	Compd.	R^1	R^2	Catalyst	**8** (*S*/*R*)	Yield [%]
1	**9α**	OCOOMe	H	$[Pd_2(dba)_3]$[a]	100:0	59[b]
2	**9β**	H	OCOOMe	$[Pd_2(dba)_3]$[a]	0:100	43[b]
3	**10α**	OH	H	$[PdCl_2(CH_3CN)_2]$[c]	100:0	89
4	**10β**	H	OH	$[PdCl_2(CH_3CN)_2]$[c]	0:100	77

[a] Toluene, 80 °C. Neocuproine was used as a ligand. [b] Triene was produced as a by-product. [c] THF, 0 °C.

of the C20 alcohol followed by reductive opening of the benzylidene acetal gave the C17 alcohol.[12] Oxidation of the primary alcohol to an aldehyde followed by a Wittig reaction gave α,β-unsaturated ester **12** in 66% yield over four steps. Reduction of the ester with DIBAL-H and oxidation with Dess–Martin periodinane afforded the desired aldehyde **2** in 92% yield over two steps. The product was identical to the aldehyde reported by Nelson et al.[5g]

The synthesis of the C1–C14 carbon chain commenced from allylic alcohol **13** (Scheme 5).[13] The routine three steps (silylation of the secondary alcohol, osmylation of the double bond, and cleavage of the diol) gave an aldehyde, which underwent Ni/Cr-pro-

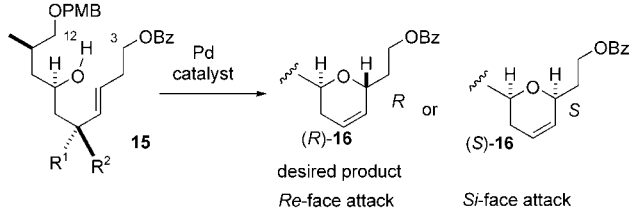


Scheme 5. Synthesis of **3**. Reagents and conditions: a) TBDMSCl, imidazole, DMF, room temperature, 97%; b) 1. OsO_4 (cat.), NMO, THF/H_2O (5:1), room temperature; 2. $NaIO_4$, THF/H_2O (5:1); 3. (*E*)-4-benzyloxy-1-iodo-1-butene, $NiCl_2/CrCl_2$ (cat.), DMSO, room temperature, 75%; c) DMP, 91%; d) BH_3·THF complex, (*S*)-CBS, THF, −40 °C, 99% (d.r. > 97:3); e) TBAF, THF, room temperature, 85%; f) $[PdCl_2(CH_3CN)_2]$ (15 mol%), benzoquinone, THF, −5 °C, 60%; g) K_2CO_3, MeOH, room temperature, 92%; h) DMP, 90%; i) CBr_4, PPh_3, CH_2Cl_2, 0 °C, 94%; j) *n*BuLi, THF, −78 °C; then $(HCHO)_n$, −78 → 0 °C, 83%; k) (O*t*Bu)Ph_2SiCl, Et_3N, CH_2Cl_2, room temperature, 99%; l) DDQ, CH_2Cl_2/buffer (pH 7) (10:1), room temperature, 87%; m) 1. DMP; 2. CBr_4, PPh_3, CH_2Cl_2, 0 °C, 78%; n) $Pd(OAc)_2$ (cat.), PPh_3, Me_3SiCH_2MgCl, THF, 50 °C, 86%; o) PPTS, THF/CH_3CN (9:1), room temperature, 99%. NMO = *N*-methylmorpholine *N*-oxide; DMSO = dimethyl sulfoxide; CBS = Corey–Bakshi–Shibata oxazaborolidine reagent; PPTS = pyridinium toluene-*p*-sulfonate.

moted addition[14] with (*E*)-4-benzoyloxy-1-iodo-1-butene to afford the allylic alcohols **14α** and **14β** as a mixture of diastereomers in 73% yield over four steps. Dess–Martin oxidation and enantioselective reduction of the enone with a combination of BH_3 and an (*S*)-oxazaborolidine ligand (CBS)[15] at −40 °C gave **14α** in 90% yield with high stereoselectivity (> 20:1). After removal of the TBDMS group, the diol **15α** was subjected to Pd^{II}-catalyzed ring formation in a 6-*endo*-trig fashion to give the desired pyran (*R*)-**16** exclusively in 60% yield.[16]

As shown in Table 2, pyran (*S*)-**16** was obtained from the alcohol (*S*)-**15β** in 56% yield under the same reaction conditions.[17] On the other hand, the Pd^0-catalyzed reaction of the corresponding carbonate did not undergo cyclization and gave mainly a diene.

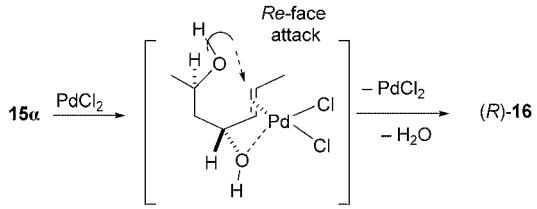
Table 2: Pd^{II}- and Pd^0-catalyzed Synthesis of (*R*)-**16** and (*S*)-**16**.



Entry	Compd.	R^1	R^2	Catalyst[a]	**16** (*R*/*S*)	Yield [%]
1	**15α**	OH	H	$[PdCl_2(CH_3CN)_2]$	100:0	60
2	**15β**	H	OH	$[PdCl_2(CH_3CN)_2]$	0:100	56
3	carbonate	OCOOMe	OH	$[Pd_2(dba)_3]$	–	–[b]

[a] Pd catalyst (15 mol%) was used in the presence of benzoquinone. [b] Diene was formed.

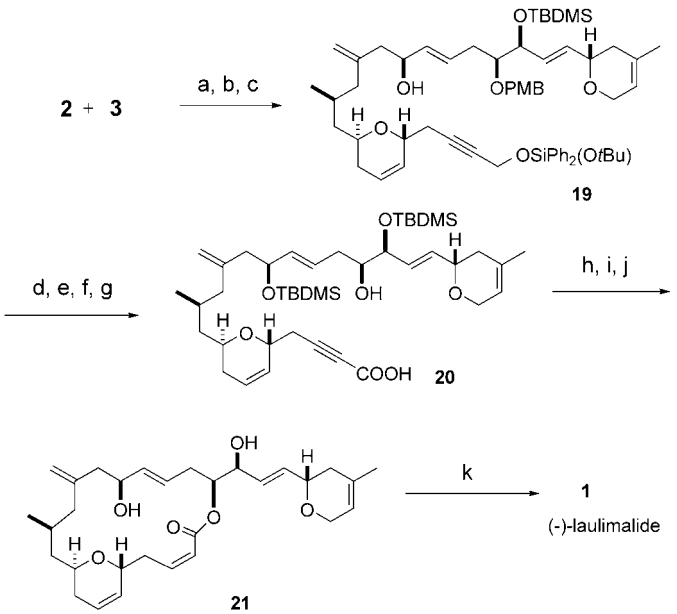
Interestingly, 6-*endo*-trig cyclization of **15α** occurs through a *syn*-S_N2' process to give the desired *trans*-(*R*)-dihydropyran ring; in this case, the hydroxy group attacks the *Re* face of the olefinic carbon atom (Scheme 6).



Scheme 6. Synthesis of (*R*)-**16** by *syn*-S_N2' reaction of **15α**.

As shown in Scheme 5, (*R*)-**16** was converted into **17** in 64% yield through the following five-step procedure: 1) deprotection of the terminal benzoate, 2) oxidation to the aldehyde, 3) homologation of the aldehyde to the 1,1-dibromoalkene, 4) debromination with *n*BuLi (2.4 equiv) and reaction of the generated lithioalkyne with paraformaldehyde, and 5) protection of the resultant alcohol with (*t*BuO)Ph_2SiCl as an orthogonal protecting group to TBDMS. The C12 PMB (*p*-methoxybenzyl) ether was transformed into a C14 allylsilane unit in five steps. Deprotection of the PMB ether with DDQ, oxidation to the aldehyde with Dess–Martin periodinane, dibromoolefination with carbon tetrabromide and triphenylphosphane gave **18** in 68% yield. The cross-coupling of the 1,1-dibromo-1-alkene **18** with Me_3SiCH_2MgCl catalyzed by 10 mol% $Pd(OAc)_2$ in the presence of triphenylphosphane gave the corresponding bis(trimethylsilylmethyl)alkene in 86% yield[18] which upon treatment with PPTS as a weak acid underwent protodesilylation to provide *exo* allylsilane **3** quantitatively.

Fragments **2** and **3** were assembled by Sakurai–Hosomi reaction promoted by $SnCl_4$ in 86% yield. Although the reaction gave a mixture of diastereomeric alcohols, oxidation of the alcohol to the enone with Dess–Martin periodinane and enantioselective reduction of the enone with BH_3 and (*R*)-CBS[15] gave the desired alcohol (*S*)-**19** in 79% yield as a single diastereomer (Scheme 7). Silylation of the alcohol and chemoselective cleavage of the (*t*BuO)Ph_2Si ether with K_2CO_3 in methanol gave propargyl alcohol in 88% yield. The C1 alcohol was converted into the seco acid in three steps: oxidation of the propargyl alcohol, deprotection of the PMB ether, and Kraus oxidation.[19] The seco acid **20**[5h] was obtained in 78% yield over the three steps. Yamaguchi lactonization, deprotection of the two silyl ethers, and partial reduction of the alkynyl group to the alkene afforded desoxylaulimalide (**21**)[5c] in 68% yield over three steps. Finally, Sharpless epoxidation with (+)-diisopropyl tartrate gave (−)-laulimalide (**1**) in 80% yield. All the physical and spectroscopic data of **1**, including specific rotation ($[\alpha]_D^{24} = -193$ ($c = 0.18$, $CHCl_3$)), are in perfect accord with those of



Scheme 7. Coupling of **2** and **3** and synthesis of **1**. Reagents and conditions: a) $SnCl_4$, CH_2Cl_2, −78 °C, 86%; b) DMP, 86%; c) BH_3·THF complex, (*R*)-CBS, THF, −40 °C, 92%; d) TBDMSCl, imidazole, DMF, room temperature, 95%; e) K_2CO_3, MeOH/THF (3:1), room temperature, 93%; f) 1. DMP; 2. DDQ, CH_2Cl_2/buffer(pH 7) (2:1), 0 °C, 80%; g) $NaClO_2$, 2-methyl-2-butene, NaH_2PO_4, THF/*t*BuOH (1:2), 0 °C, 98%; h) Yamaguchi lactonization, 88%; i) HF·py, CH_3CN, room temperature, quant. j) Lindlar cat., H_2, quinoline, EtOAc/1-hexene (1:1), room temperature, 77%; k) Sharpless epoxidation conditions, (+)-diisopropyl tartrate, 80%.

the natural product as well as those previously reported.[5a–c,h]

In conclusion, we have completed the asymmetric total synthesis of (−)-laulimalide based on the novel Pd^{II}- and Pd^0-catalyzed stereospecific ring formation of a 3,6-dihydro[2*H*]-pyran system. We believe that this method should be useful for the synthesis of not only **1** but also of a variety of other marine natural products that contain the 3,6-dihydro[2*H*]-pyran unit.

Experimental Section

3,6-Dihydro[2*H*]pyran formation (representative reaction): A mixture of **10** (1 mmol) and $[PdCl_2(CH_3CN)_2]$ (0.1 mmol) in THF (10 mL) was stirred for 3 h at 0 °C. After concentration, the residue was purified by chromatography on silica gel, eluted with EtOAc in hexane (20%) to give (*S*)-**8** as a colorless oil in 89% yield. $R_f = 0.36$ (20% EtOAc in hexane); $[\alpha]_D^{24} = -61.8$ ($c = 0.11$, MeOH); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 1.40$ (3H, s), 1.40 (3H, s), 1.69 (3H, brs), 1.77–1.95 (3H, m), 1.99–2.08 (1H, m), 3.51–3.63 (2H, m), 3.80 (3H, s), 3.83 (1H, td, $J = 8.2$ and 4.0 Hz), 4.00–4.09 (2H, m), 4.11–4.22 (2H, m), 4.43 (2H, s), 5.41 (1H, brs), 5.70 (1H, ddd, $J = 15.6$, 7.5, and 1.3 Hz), 5.87 (1H, ddd, $J = 15.6$, 5.4, and 0.5 Hz), 6.86 (2H, d, $J = 8.8$ Hz), 7.25 ppm (2H, d, $J = 8.8$ Hz); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 22.9$, 26.9, 27.2, 32.0, 35.6, 55.2, 65.6, 66.7, 72.6, 73.1, 77.8, 81.9, 108.6, 113.7, 119.6, 127.4, 129.2, 130.5, 131.3, 135.4, 159.1 ppm; IR (neat): $\tilde{\nu} = 1613$, 1514 cm^{-1}; MS (20 eV): *m*/*z* (%): 388 (0.4) [M^+], 370 (1), 209 (6), 160 (10), 136 (36), 121 (100); HRMS (20 eV): calcd for $C_{23}H_{32}O_5$: 388.2250, found: 388.2251. (*R*)-**8**: 77% yield; its physical and spectroscopic data is described in the Supporting Information.

Reaction of **15**: A mixture of **15** (3 mmol) and $[PdCl_2(CH_3CN)_2]$ (0.45 mmol) in THF (60 mL) was stirred for 1 h at −5 °C. After addition of benzoquinone (0.9 mmol), the mixture was stirred for 2 days at room temperature. The mixture was diluted with hexane (70 mL), and $NaBH_4$ (1 mmol) was added to decompose the remaining benzoquinone. The standard workup and purification by silica-gel column chromatography eluted with EtOAc in hexane (10%) gave (*R*)-**16** as a colorless oil in 60% yield. $R_f = 0.76$ (30% EtOAc in hexane); $[\alpha]_D^{24} = -29.5$ ($c = 0.74$, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 0.97$ (3H, d, $J = 6.8$ Hz), 1.23 (1H, ddd, $J = 14.1$, 9.5, and 3.5 Hz), 1.71 (1H, ddd, $J = 14.1$, 9.7, and 4.2 Hz), 1.89–2.13 (5H, m), 3.24 (1H, dd, $J = 9.1$ and 6.5 Hz), 3.33 (1H, dd, $J = 9.1$ and 6.0 Hz), 3.75–3.82 (1H, m), 3.79 (3H, s), 4.38–4.52 (3H, m), 4.43 (2H, s), 5.68–5.73 (1H, m), 5.82–5.88 (1H, m), 6.86 (2H, d, $J = 6.8$ Hz), 7.25 (2H, d, $J = 8.6$ Hz), 7.40–7.45 (2H, m), 7.52–7.57 (1H, m), 8.02–8.06 ppm (2H, m); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 16.8$, 29.7, 31.3, 33.0, 39.4, 55.3, 61.9, 65.2, 69.2, 72.5, 75.9, 113.7, 124.8, 128.3, 129.0, 129.1, 129.6, 130.4, 130.9, 132.9, 159.0, 166.5 ppm; IR (neat): $\tilde{\nu} = 2955$, 2930, 1716, 1613, 1513, 1276, 1249, 1112, 1036 cm^{-1}; MS (20 eV): *m*/*z* (%): 424 (2) [M^+], 303 (2), 285 (3), 204 (11), 181 (44), 121 (100); HR-MS (20 eV): calcd for $C_{26}H_{32}O_5$: 424.2250; found: 424.2249. (*S*)-**16**: 56% yield; its physical and spectroscopic data is described in the Supporting Information.

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[1] a) E. Quinoa, Y. Kakou, P. Crews, *J. Org. Chem.* **1988**, *53*, 3642–3644; b) D. G. Corley, R. Herb, R. E. Moore, P. J. Scheuer, V. J. Paul, *J. Org. Chem.* **1988**, *53*, 3644–3646; c) C. W. Jefford, G. Bernardinelli, J. Tanaka, T. Higa, *Tetrahedron Lett.* **1996**, *37*, 159–162.

[2] S. L. Mooberry, G. Tien, A. H. Hernandez, A. Plubrukarn, B. S. Davidson, *Cancer Res.* **1999**, *59*, 653–660.

[3] a) D. E. Pryor, A. O'Brate, G. Bilcer, J. F. Diaz, Y. Wang, Y. Wang, M. Kabaki, M. K. Jung, J. M. Andreu, A. K. Ghosh, P. Giannakakou, E. Hamel, *Biochemistry* **2002**, *41*, 9109–9115; b) E. J. Gapud, R. Bai, A. K. Ghosh, E. Hamel, *Mol. Pharmacol.* **2004**, *66*, 113–121; c) O. Pineda, J. Farras, L. Maccari, F. Manetti, M. Botta, J. Vilarrasa, *Bioorg. Med. Chem. Lett.* **2004**, *14*, 4825–4829.

[4] An excellent review for (−)-laulimalide; see, J. Mulzer, E. Öhler, *Chem. Rev.* **2003**, *103*, 3753–3786.

[5] Total syntheses; see, a) A. K. Ghosh, Y. Wang, *J. Am. Chem. Soc.* **2000**, *122*, 11027–11028; b) I. Paterson, C. De Savi, M. Tudge, *Org. Lett.* **2001**, *3*, 3149–3152; c) J. Mulzer, E. Öhler, *Angew. Chem.* **2001**, *113*, 3961–3964; *Angew. Chem. Int. Ed.* **2001**, *40*, 3842–3846; d) P. A. Wender, S. G. Hegde, R. D. Hubbard, L. Zhang, *J. Am. Chem. Soc.* **2002**, *124*, 4956–4957; e) M. T. Crimmins, M. G. Stanton, S. P. Allwein, *J. Am. Chem. Soc.* **2002**, *124*, 5958–5959; f) D. R. Williams, L. Mi, R. J. Mullins, R. E. Stites, *Tetrahedron Lett.* **2002**, *43*, 4841–4844; g) S. G. Nelson, W. S. Cheung, A. J. Kassick, M. A. Hilfiker, *J. Am. Chem. Soc.* **2002**, *124*, 13654–13655; h) B. M. Gallagher, Jr., F. G. Fang, C. W. Johannes, M. Pesant, M. R. Tremblay, H. Zhao, K. Akasaka, X. Li, J. Liu, B. A. Littlefield, *Bioorg. Med. Chem. Lett.* **2004**, *14*, 575–579.

[6] J. Uenishi, M. Ohmi, K. Matsui, M. Iwano, *Tetrahedron* **2005**, *61*, 1971–1979.

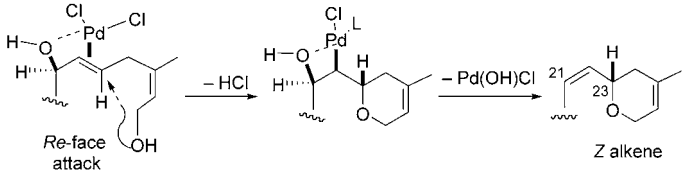
[7] The compound **7α** was unreactive under these (and even harsher) conditions.

[8] A. Pfaltz, M. Lautens in *Comprehensive Asymmetric Catalysis*, *Vol. II* (Eds.: E. N. Jacobsen, A. Pfaltz, H. Yamamoto), Springer,

Berlin, **1999**, pp. 833–884; J. Tsuji, *Palladium Reagents and Catalysts*, Wiley, Chichester, **1995**.

[9] For Pd^{II}-catalyzed intramolecular C–O bond-forming reaction, see: T. Hosokawa, S. Murahashi in *Handbook of Organopalladium Chemistry for Organic Synthesis*, *Vol. 2* (Ed: E.-i. Negishi), Wiley, New York, **2002**, pp. 2169–2192.

[10] If the alternative Pd π complex is formed as shown below, though it is unfavorable owing to allylic strain, and the oxygen nucleophile were to attack the olefinic carbon atom from the other side of the Pd π complex, the desired 23*S* stereogenic center would be generated. However, the successive *syn* elimination of Pd(OH)Cl would then afford the 21*Z* alkenyl product.



[11] Interestingly, Pd^{II}-catalyzed piperidine ring formation gave the opposite stereochemistry in an *anti*-S_N2'-type reaction: Y. Hirai, M. Nagatsu, *Chem. Lett.* **1994**, 21–22.

[12] Although the *O*-silyl group at C20 was desilylated partially under these conditions, acetylation of C17-OH followed by silylation of C20-OH with TBDMSCl and methanolysis of the acetate led to the primary alcohol in 80% yield over three steps.

[13] Compound **13** was prepared from methyl (*S*)-3-hydroxy-2-methylpropionate according to: A. Ahmed, E. K. Hoegenauer, V. S. Enev M. Hanbauer, H. Kaehlig, E. Öhler, J. Mulzer, *J. Org. Chem.* **2003**, *68*, 3026–3042.

[14] a) H. Jin, J. Uenishi, W. J. Christ, Y. Kishi, *J. Am. Chem. Soc.* **1986**, *108*, 5644–5646; b) K. Takai, M. Tagashira, T. Kuroda, K. Oshima, L. Utimoto, H. Nozaki, *J. Am. Chem. Soc.* **1986**, *108*, 6048–6050.

[15] For enantioselective reduction through CBS reduction, see: E. J. Corey, R. K. Bakshi, S. Shibata, *J. Am. Chem. Soc.* **1987**, *109*, 5551–5553; for the reduction of an enone with BH_3 and (*R*)- or (*S*)-2-methyl-oxazaborolidine, see: H. Motoyoshi, K. Ishigami, T. Kitahara, *Tetrahedron* **2001**, *57*, 3899–3908.

[16] For 5-*endo*-trig cyclization in dihydrofuran synthesis, see: S. Saito, T. Hara, N. Takahashi, M. Hirai, T. Moriwake, *Synlett* **1992**, 237–238.

[17] The stereochemistry of **15α** and **15β** was confirmed by NOE experiments after their conversion into acetonide derivatives.

[18] J. Uenishi, M. Ohmi, *Heterocycles* **2003**, *61*, 365–376.

[19] G. A. Kraus, B. Roth, *J. Org. Chem.* **1980**, *45*, 4825–4830.

