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Efficient construction of novel α-keto spiro ketal and the total synthesis of (±)-terreinol

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Abstract—The first total synthesis of (±)-terreinol is described. An intramolecular Pd(II)-catalyzed cycloisomerization of a 2-(1′-alkynyl)benzyl alcohol via an apparent 6-*endo* diagonal pathway led to the 1*H*-isochromene ring system, which was further converted to the desired spiro ketal via an iodine-mediated intramolecular spiro-cyclization.

1. Introduction

Fungi have been one of the main resources of a wide variety of complex natural products possessing attractive biological activities.[1] For example, lovastatin (mevinolin) derived from fungus *Aspergillus terreus* is now used as a cholesterol lowering agent.[2] Terreinol was isolated more recently as a novel metabolite by Marsaioli and co-workers in an effort to screen enzymatic activity in malt extracts from cultures of Brazilian strains of *A. terreus*.[3a] Its absolute configuration was determined thereafter by ^{1}H and ^{13}C NMR experiments, allowing assignment of the *R* configuration for terreinol.[3b] This apparently simple molecule is structurally distinguished by a highly oxygenated isochromene core bearing a novel dioxa-spiro ketal. Attracted by its unique structure and the interesting bioactivities of similar spiro-cyclic compounds, we sought to establish an efficient route for the synthesis of terreinol by using readily available materials. Herein, we report our recent achievement of the first total synthesis of (±)-terreinol, in which an intramolecular Pd(II)-catalyzed cycloisomerization and an intramolecular iodoetherification were employed as key steps.

2. Results and discussion

Our strategy for the synthesis of terreinol was based on two major considerations as shown in Figure 1. First, the spiro ketal core of **B** was to be derived from an intramolecular haloetherification reaction, while, the 1*H*-isochromene ring system of **C** was to be elaborated by an intramolecular Pd(II)-catalyzed cycloisomerization of precursor **D**. It was anticipated that the six-member ring would be formed preferentially over the five-member ring. Facile removal of the phenolic hydroxyl protections must be carefully considered in the last step. Finally, the fully functionalized precursor benzylalcohol derivative **D** could be easily prepared from readily available starting materials, such as aryl bromide **E** and terminal alkyne, by Sonogashira coulping reaction.

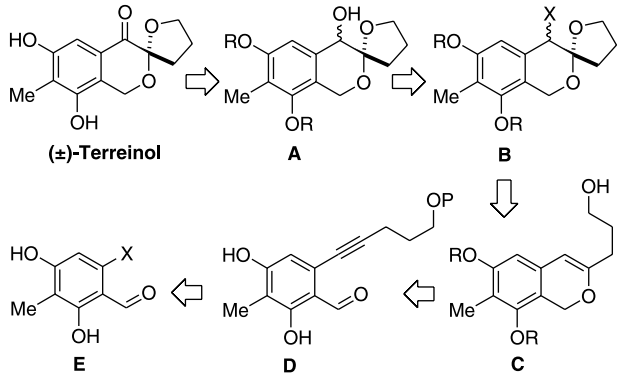

Figure 1. Retrosynthetic analysis of (±)-terreinol.

As outlined in Scheme 1, commencing with the commercially available 2-methylresorcinol, 2-bromobenzaldehyde **8** was prepared using a modification of the recently reported protocol by Porco et al.[4] Accordingly,

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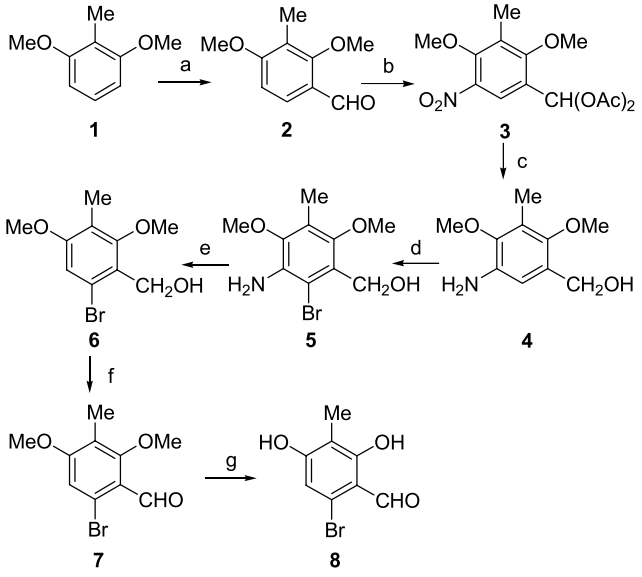
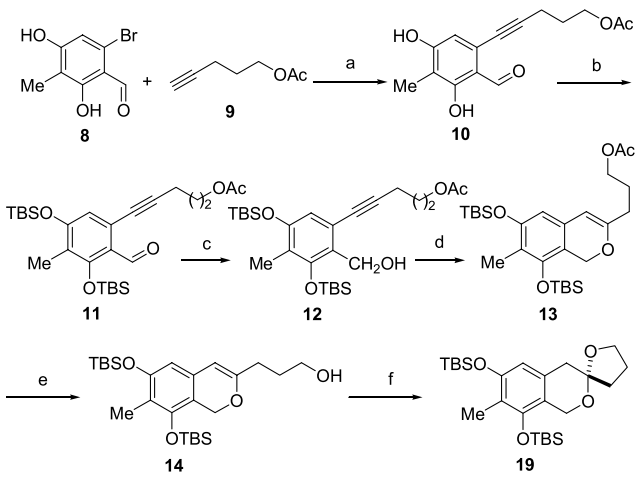


Scheme 1. Reagents and conditions: (a) $POCl_3$, DMF, 60 °C, 90%; (b) $Cu(NO_3)_2 \cdot 3H_2O$, Ac_2O, 94%; (c) Raney Nickel (50% in H_2O), H_2, THF, 98%; (d) NBS (1.1 equiv), $CHCl_3$, rt, 92%; (e) Concd HCl, THF/H_2O, $NaNO_2$ then urea, 50% H_3PO_2, 89%; (f) PCC, 4 Å sieves, CH_2Cl_2, 0 °C to rt, 87%; (g) BBr_3, CH_2Cl_2, −78 °C to rt, 94%.

2,6-dimethoxytoluene **1** was derived from 2-methylresorcinol and acylated to give aldehyde **2**. Nitration of benzaldehyde **2** was carried out with $Cu(NO_3)_2$ in acetic anhydride to give the expected geminal diacetate **3**. Raney nickel-catalyzed reduction of the nitro group and simultaneously removal of the geminal diacetate were performed in facile fashion in THF under a H_2 atmosphere. Selective bromination of the resulting 3-aminobenzyl alcohol **4** was achieved using NBS in $CHCl_3$ to give *o*-bromoaniline **5** in excellent yield. Reductive removal of the amino group of **5** was carried out by diazotization followed by H_3PO_2-based sediazotization in situ. Oxidation of the resultant 6-bromo-2,4-dimethoxy-3-methylbenzyl alcohol **6** occurred smoothly by using PCC and 4 Å molecular sieves in anhydrous dichloromethane to afford the corresponding benzaldehyde **7**. Finally, treatment of **7** with BBr_3 afforded 2-bromobenzaldehyde **8** in high yield. All these improvements have the advantages of more stable intermediates, high yield for each step, and ease of operation and reduplication.



Scheme 2. Reagents and conditions: (a) 5 mol% $Pd(PPh_3)_4$, CuI, 4-pentynyl acetate **9**, Et_3N, DMF, 70 °C, 92%; (b) TBSCl, imid, DMF, 87%; (c) $NaBH_4$, EtOH, 0 °C, 5 min, 75%; (d) 10 mol% $PdCl_2(PPh_3)_2$, 1,4-dioxane, 85 °C, 72%; (e) K_2CO_3, MeOH, rt, 97%; (f) H^+, $CDCl_3$, rt, 24 h, quantitative.

The functionalized cycloisomerization precursor **10** was next prepared by a Sonogashira coupling,[5] which linked aryl bromide **8** and terminal acetylene **9**[6] (Scheme 2). The phenolic hydroxyls were then protected as TBS ethers **11**, Treatment of benzylaldehye **11** with $NaBH_4$ in ethanol at 0 °C gave the corresponding benzyl alcohol **12**. With this precursor in hand, construction of the 1*H*-isochromene structure by intramolecular ring-closure reaction of **12** was investigated. Earlier studies on this type of cycloisomerization revealed that both the substituent pattern of the substrates and the reaction conditions could influence the reaction leading either toward the 5-*exo-dig* cyclization or the 6-*endo-dig* cyclization products.[7] A short list of Pd(II) catalysts (Table 1) were screened on **12** for their ability to promote the desired 6-*endo* cycloisomerization. To our delight, 10 mol% of $PdCl_2(PPh_3)_2$ in 1,4-dioxane at 85 °C worked very well and 1*H*-isochromene **13** was obtained as a single isomer in satisfactory yield. It is noteworthy that the unprotected phenolic benzylalcohol didn't produce any desired cycloisomerized product under such conditions. Other Pd(II) species and conditions also gave **13**, however, in lower yields or under longer reaction times (see Table 1). Theoretically, the five-member-ring product might be also produced under these conditions. However, no evidence of five-member-ring product was detected during our investigations. Treatment of acetate **13** with K_2CO_3 in methanol at rt afforded the corresponding alcohol **14** in high yield. It is noteworthy that this compound was quantitatively converted to spiro ketal **19**[8] in $CDCl_3$ (weakly acidic) when left in NMR tube over 24 h.

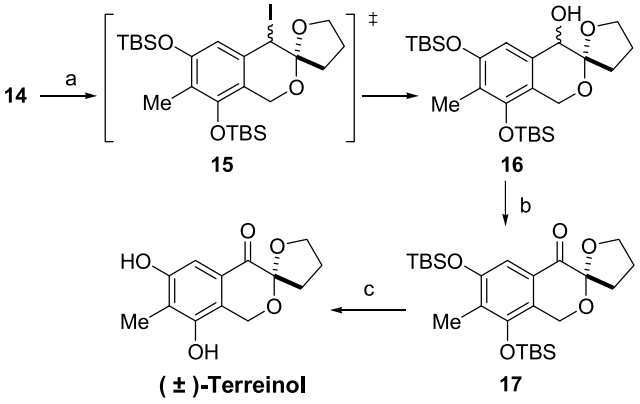
Table 1. Synthesis of 1*H*-isochromene **13** by Pd(II)-catalyzed cycloisomerization of **12**

Entry[a]	Catalyst (mol%)	*T* (°C)	Time (h)	Product (%)
1	10% $PdCl_2$	85	1.0	64
2	10% $Pd(OAc)_2$	85	5.0	14
3	10% $PdCl_2(PPh_3)_2$	85	1.5	72
4	5% $PdCl_2(PPh_3)_2$	85	6.0	68
5	5% PdI_2	85	4.0	64
6	10% $Pd(PhCN)_2Cl_2$	85	1.5	60

[a] The reactions were all carried out in 1,4-dioxane as the solvent.

The final key transformation to achieve our ultimate synthetic object was to establish the spiro ketal functionality. It was anticipated that an intramolecular iodoetherification reaction could be utilized for this key transformation. It is well known that iodoetherification is a powerful method for the construction of THF rings from the corresponding γ-hydroxyalkenes. This is also an efficient method to functionalize olefinic double bonds.[9] Treatment of compound **14** with 2 equiv of iodine in a mixture of CH_3CN and aq $NaHCO_3$ (10:1, v:v) at ambient temperature gave the desired spiro ketal **15**. The iodide **15** was immediately substituted by hydroxide in situ to furnish **16** as a mixture of isomers (ca. 35:1) at rt in 86% overall yield (from **14**). Dess–Martin oxidation[10] of the resulting

mixture afforded **17** quantitatively as a single product. Finally, global deprotection[11] was achieved using TBAF in THF, to give racemic terreinol in excellent yield (Scheme 3). Data for terreinol obtained by this route were identical with those reported for natural material.[3]



Scheme 3. Reagents and conditions: (a) I_2, CH_3CN, aq $NaHCO_3$, rt, 86%; (b) Dess–Martin periodinane, CH_2Cl_2, 97%; (c) TBAF, THF, rt, 98%.

3. Conclusions

In conclusion, we have disclosed the first total synthesis of the fungal metabolite terreinol. The palladium(II)-catalyzed cycloisomerization of 2-(1′-alkynyl)benzyl alcohol **12** efficiently furnished the key precursor 1*H*-isochromene **13**. The spiro ketal was subsequently elaborated by iodoetherification of alcohol **14**. Further investigations including the enantioselective synthesis of the corresponding spiro cycles and bioactivity studies of this novel metabolite are currently underway.

4. Experimental

4.1. General methods

^1H NMR spectra were recorded at 300 or 400 MHz at ambient temperature with $CDCl_3$ as the solvent unless otherwise stated. ^{13}C NMR spectra were recorded at 100 MHz at ambient temperature with $CDCl_3$ as the solvent unless otherwise stated. All melting points were uncorrected. Infrared (IR) spectra were obtained using a Fourier transform infrared spectrometer (FTIR). Flash column chromatography was performed on silica gel (10–40 μm) using a mixture of petroleum ether and ethyl acetate as the eluent.

4.1.1. (5-Amino-2,4-dimethoxy-3-methylphenyl)methanol (4). A solution of **3** (8.5 g, 26.0 mmol) in 150 mL THF was treated with Raney Nickel (50% in H_2O, 10.0 g). The resulting mixture was hydrogenated under H_2 at rt and the reaction process was monitored by TLC. After completion of the reaction, the mixture was filtered through Celite and washed with ethyl acetate. The filtrate was concentrated under reduced pressure to give **4** (5.0 g, 98%) as a pale yellow solid, which was employed in the next step without further purification. Recrystallization of the product from hexane and ethyl acetate afforded colorless crystal for characterization. Mp 75–77 °C. ^1H NMR (300 MHz, $CDCl_3$): δ 6.58 (1H, s), 4.59 (2H, s), 3.72 (3H, s), 3.71 (3H, s), 3.60–2.80 (2H, br s), 2.21 (3H, s) ppm. IR (KBr): ν_{max} 3394, 3251, 3145, 1598, 1485, 1419, 1212, 1101, 1008, 834 cm^{-1}. ESI-MS (*m*/*z*): 198 ($M+H^+$). Anal. Calcd for $C_{10}H_{15}NO_3$: C, 60.90; H, 7.67; N, 7.10. Found: C, 61.06; H, 7.31; N, 7.09.

4.1.2. (3-Amino-2-bromo-4,6-dimethoxy-5-methylphenyl) methanol (5). To a solution of **4** (1.0 g, 5.1 mmol) in $CHCl_3$ (20 mL) was added NBS (990 mg, 5.6 mmol). The mixture was stirred at rt for 5 min, and then aq $Na_2S_2O_3$ solution was added to quench the reaction. The mixture was extracted with ethyl acetate for three times and combined organic layers were washed extensively with H_2O and finally brine. The organic extracts were dried over Na_2SO_4, filtered, concentrated and the residue was purified by silica gel column (hexane/ethyl acetate = 4:1) to afford **5** (1.3 g, 92%) as a pale yellowish oil. ^1H NMR (300 MHz, $CDCl_3$): δ 4.76 (2H, s), 4.10 (2H, br s), 3.72 (3H, s), 3.71 (3H, s), 2.50 (1H, br s), 2.17 (3H, s) ppm. IR (film): ν_{max} 3455, 3361, 2941, 1608, 1575, 1459, 1415, 1247, 1195, 1126, 1107, 1006, 981 cm^{-1}. HRMS (ESI, *m*/*z*) calcd for $C_{10}H_{15}BrNO_3$ ($M+H^+$): 276.0235; found: 276.0231.

4.1.3. Acetic acid 5-(2-formyl-3,5-dihydroxy-4-methyl phenyl)pent-4-ynyl ester (10). To a mixture of 2-bromobenzaldehyde **8** (20 g, 86.6 mmol), alkyne **9** (13 g, 103.9 mmol), $Pd(PPh_3)_4$ (5.0 g, 4.3 mmol), CuI (840 mg, 4.4 mmol) in degassed DMF (70 mL) was added Et_3N (36 mL) under inert atmosphere. The resulting mixture was heated and then stirred at 70 °C for about 6 h. The solvent was removed under reduced pressure and the residue was purified directly on silica gel column (hexane/ethyl acetate = 5:1). The obtained crude product was then crystallized from hexane and ethyl acetate, affording **10** (22 g, 92%) as a white solid. Mp 97–99 °C. ^1H NMR (300 MHz, $CDCl_3$): δ 12.27 (1H, s), 10.16 (1H, s), 7.50 (1H, br s), 6.51 (1H, s), 4.25 (2H, t, J = 6.3 Hz), 2.56 (2H, t, J = 6.9 Hz), 2.11 (3H, s), 2.10 (3H, s), 2.01–1.92 (2H, m) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 195.0, 172.1, 163.1, 161.40, 161.36, 126.8, 114.2, 112.6, 112.2, 95.2, 63.5, 27.6, 21.0, 16.4, 7.2. IR (KBr): ν_{max} 3379, 1711, 1635, 1609, 1588, 1422, 1367, 1303, 1251, 1139, 1107, 1049, 834, 769, 586 cm^{-1}. ESI-MS (*m*/*z*): 274 ($M+H^+$). Anal. Calcd for $C_{15}H_{16}O_5$: C, 65.21; H, 5.84. Found: C, 65.18; H, 5.81.

4.1.4. Acetic acid 5-[3,5-bis(*tert*-butyldimethylsilanyl oxy)-2-formyl-4-methylphenyl]pent-4-ynyl ester (11). A mixture of phenol **10** (2.0 g, 5.9 mmol), imidazole (2.4 g, 35.5 mmol) and TBSCl (4.5 g, 29.6 mmol) in anhydrous DMF (6.0 mL) was stirred at rt for about 4 h under N_2 atmosphere. The mixture was then diluted with ethyl acetate (100 mL) and water (30 mL). The organic layer was separated and washed with H_2O (4×30 mL), brine, dried over Na_2SO_4, filtered, and concentrated. The crude product was purified by silica gel column (hexane/ethyl acetate = 50:1) to give **11** (2.6 g, 87%) as a colorless oil. ^1H NMR (300 MHz, $CDCl_3$): δ 10.31 (1H, s), 6.61 (1H, s), 4.28 (2H, t, J = 6.3 Hz), 2.59 (2H, t, J = 6.9 Hz), 2.09 (3H, s), 2.08 (3H, s), 2.07–1.98 (2H, m), 1.06 (9H, s), 1.04 (9H, s), 0.28 (6H, s), 0.15 (6H, s) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 189.4, 171.0, 159.2, 157.5, 123.8, 123.1, 122.2, 118.2, 93.9,

79.2, 63.2, 27.7, 25.9 (×3), 25.7 (×3), 20.9, 18.6, 18.3, 16.6, 10.9, −3.6 (−2), −4.1 (×2) ppm. IR (film): ν_{max} 2957, 2932, 1745, 1696, 1576, 1548, 1473, 1237, 1153, 840, 827 cm^{-1}. HRMS (ESI, *m/z*) calcd for $C_{27}H_{45}O_5Si_2$ ($M+H^+$): 505.2806; found: 505.2804.

4.1.5. Acetic acid 5-[3,5-bis(*tert*-butyldimethylsilanyl oxy)-2-hydroxymethyl-4-methylphenyl]pent-4-ynyl ester (12). To a pre-cooled solution of aldehyde **11** (1.5 g, 3.0 mmol) in ethanol (40 mL) was added $NaBH_4$ (170 mg, 4.5 mmol) at 0 °C. 5 min later, aq NH_4Cl was added slowly to quench the reaction. The mixture was then diluted with ethyl acetate (200 mL). The organic layer was separated and washed with H_2O and brine, dried over Na_2SO_4, filtered, concentrated. The residue was purified by silica gel column chromatography (hexane/ethyl acetate=4:1) to give **12** (1.1 g, 75%) as a colorless oil. ^1H NMR (300 MHz, $CDCl_3$): δ 6.56 (1H, s), 4.71 (2H, d, J=6.3 Hz), 4.24 (2H, t, J=6.3 Hz), 2.55 (2H, t, J=7.2 Hz), 2.45 (1H, t, J=6.3 Hz), 2.07 (s, 3H), 2.06 (s, 3H), 2.00–1.91 (m, 2H), 1.04 (s, 9H), 1.00 (s, 9H), 0.21 (s, 6H), 0.18 (s, 6H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 171.1, 154.1, 152.6, 127.1, 121.8, 121.0, 116.5, 91.9, 79.6, 63.1, 58.9, 27.9, 26.1 (×3), 25.8 (×3), 20.9, 18.7, 18.3, 16.4, 11.9, −3.6 (×2), −4.2 (×2) ppm. IR (film): ν_{max} 3600, 2958, 2860, 1744, 1593, 1556, 1472, 1254, 1145, 1114, 898, 828, 782 cm^{-1}. HRMS (ESI, *m/z*) calcd for $C_{27}H_{46}O_5Si_2Na$ ($M+Na^+$): 529.2781; found 529.2774.

4.1.6. Acetic acid 3-[6,8-bis(*tert*-butyldimethylsilanyl oxy)-7-methyl-1*H*-2-benzopyran-3-yl]propyl ester (13). To a mixture of **12** (120 mg, 0.24 mmol) in 1,4-dioxane (60 mL) was added $PdCl_2(PPh_3)_2$ (17 mg, 0.024 mmol) under N_2. The mixture was warmed to 85 °C and stirred at same temperature for 4 h. The solvent was removed under reduced pressure, and the residue was purified directly on silica gel column (hexane/ethyl acetate=20:1) to afford **13** (86 mg, 72%) as a colorless oil. ^1H NMR (300 MHz, $CDCl_3$): δ 6.12 (1H, s), 5.56 (1H, s), 4.98 (2H, s), 4.13 (2H, t, J=6.6 Hz), 2.26 (2H, t, J=7.5 Hz), 2.06 (3H, s), 2.03 (3H, s), 1.95–1.86 (2H, m), 1.03 (9H, s), 1.01 (9H, s), 0.20 (6H, s), 0.15 (6H, s) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 171.1, 156.7, 154.3, 149.3, 130.2, 118.3, 111.2, 107.5, 101.7, 65.0, 63.9, 30.1, 26.2, 26.0 (×3), 25.8 (×3), 20.9, 18.6, 18.3, 11.4, −3.5 (×2), −4.2 (×2) ppm. IR (film): ν_{max} 2931, 2860, 1650, 1604, 1566, 1474, 1423, 1257, 1127, 840, 780 cm^{-1}. MALDI-FTMS (DHB, *m/z*) calcd for $C_{27}H_{46}O_5Si_2Na$ ($M+Na^+$): 529.2781; found 529.2761.

4.1.7. 3-[6,8-Bis(*tert*-butyldimethylsilanyloxy)-7-methyl-1*H*-2-benzopyran-3-yl]propan-1-ol (14). To a solution of **13** (80 mg, 0.16 mmol) in methanol (10 mL) was added K_2CO_3 (87 mg, 0.63 mmol). The whole mixture was stirred at rt for 2 h. The mixture was then diluted with CH_2Cl_2 (100 mL) and saturated NH_4Cl solution (20 mL). The organic layer was separated and then washed with H_2O and brine, dried over Na_2SO_4, filtered, concentrated. The residue was purified by silica gel chromatography (hexane/ethyl acetate=4:1) to afford alcohol **14** (71 mg, 97%) as a colorless oil. ^1H NMR (300 MHz, $CDCl_3$): δ 6.13 (1H, s) 5.58 (1H, s), 4.99 (2H, s), 3.72 (2H, t, J=5.7 Hz), 2.29 (2H, t, J=7.2 Hz), 2.03 (3H, s), 1.88–1.79 (2H, m), 1.04 (9H, s), 1.01 (9H, s), 0.20 (6H, s), 0.15 (6H, s) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 157.2, 154.3, 149.2, 130.2, 118.4, 111.1, 107.5, 101.7, 64.9, 62.3, 30.2, 30.0, 25.9 (×3), 25.8 (×3), 18.5, 18.3, 11.4, −3.6 (×2), −4.2 (×2) ppm. IR (film): ν_{max} 3464, 2932, 2860, 1744, 1652, 1604, 1567, 1474, 1423, 1256, 1128, 1049, 973, 840, 781 cm^{-1}. MALDI-FTMS (DHB, *m/z*) calcd for $C_{25}H_{44}O_4Si_2Na$ ($M+Na^+$): 487.2676; found 487.2683.

4.1.8. Compound 16. To a solution of alcohol **14** (80 mg, 0.17 mmol) in CH_3CN (50 mL) and aq $NaHCO_3$ (5 mL) was added iodine (87 mg, 0.34 mmol). The mixture was stirred at rt overnight, and then quenched by aq $Na_2S_2O_3$, extracted with ethyl acetate (3×50 mL). The combined organic phases were washed with H_2O and brine, dried over anhydrous Na_2SO_4, filtered and concentrated. The residue was purified on silica gel column (hexane/ethyl acetate=5:1) to give **16** (72 mg, 86%) as mixture of two isomers. Data of the major isomer (70 mg): ^1H NMR (300 MHz, $CDCl_3$): δ 6.55 (1H, s), 4.69 (2H, s), 4.16 (1H, d, J=10.2 Hz), 4.05–4.00 (2H, m), 2.18–2.14 (2H, m), 2.05 (3H, s), 2.00–1.96 (2H, m), 1.01 (18H, s), 0.22 (12H, s) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 153.8, 149.9, 132.7, 120.3, 117.7, 113.1, 107.2, 69.6, 69.4, 60.4, 34.5, 26.1 (×3), 25.8 (×3), 23.8, 18.8, 18.3, 11.4, −2.8, −3.0, −4.1, −4.2 ppm. IR (film): ν_{max} 3423, 2931, 2860, 1608, 1585, 1474, 1256, 1126, 1041, 904, 833, 780 cm^{-1}. HR-MS (ESI, *m/z*) calcd for $C_{25}H_{44}O_5Si_2Na$ ($M+Na^+$) 503.2625; found 503.2621.

4.1.9. Compound 17. To a solution of alcohol **16** (58 mg, 0.12 mmol) in dichloromethane (10 mL) was added Dess–Martin periodinane[10] (76 mg, 0.18 mmol) at rt. The reaction was stirred for 3 h and quenched by adding aq $Na_2S_2O_3$ and aq $NaHCO_3$. Stirring was continued until the mixture turned clear. The mixture was extracted with ethyl acetate (3×50 mL). The combined organic layers were washed with water and brine, dried over Na_2SO_4, filtered, concentrated. Purification on silica gel column (hexane/ethyl acetate=10:1) gave **17** (56 mg, 97%) as a colorless oil. ^1H NMR (400 MHz, $CDCl_3$): δ 7.17 (1H, s), 5.01 (1H, d, J=15.4 Hz), 4.74 (1H, d, J=15.4 Hz), 4.14–4.06 (1H, m), 4.04 (1H, dd, J=14.6, 7.7 Hz), 2.73 (1H, dt, J=12.9, 8.8 Hz), 2.16–2.08 (2H, m), 2.12 (3H, s), 1.88 (1H, ddd, J=12.7, 8.1, 4.4 Hz), 1.03 (9H, s), 1.01 (9H, s), 0.234 (3H, s), 0.230 (3H, s), 0.20 (3H, s), 0.19 (3H, s) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 188.9, 154.2, 149.7, 127.7, 127.0, 126.4, 109.8, 105.4, 70.2, 59.1, 33.1, 26.0 (×3), 25.8 (×3), 24.9, 18.7, 18.3, 12.1, −2.9, −3.3, −4.3 (×2) ppm. IR (film): ν_{max} 2958, 2932, 1702, 1597, 1467, 1321, 1261, 1133, 1050, 886, 829, 782 cm^{-1}. HR-MS (ESI, *m/z*) calcd for $C_{25}H_{42}O_5Si_2Na$ ($M+Na^+$) 501.2468; found 501.2463.

4.1.10. (±)-Terreinol. A solution of compound **17** (42 mg, 0.088 mmol) in THF (10 mL) was treated with TBAF (1.0 M in THF, 170 μL, 0.17 mmol) at rt for 10 min. The solvent was removed under reduced pressure. The residue was purified directly on silica gel column (hexane/ethyl acetate=5:1) to afford racemic terreinol (22 mg, 98%) as a white wax. ^1H NMR (400 MHz, CD_3OD): δ 6.97 (1H, s), 4.94 (1H, d, J=15.7 Hz), 4.74 (1H, d, J=15.7 Hz), 4.08–4.03 (1H, m), 3.97 (1H, dd, J=15.1, 7.6 Hz), 2.63 (1H, dt, J=12.8, 8.8 Hz), 2.13 (3H, s), 2.13–2.09 (1H, m), 2.04–2.00 (1H, m), 1.89 (1H, ddd, J=12.7, 8.1,

4.5 Hz) ppm. ^{13}C NMR (100 MHz, CD_3OD): δ 191.2, 157.1, 152.8, 128.3, 123.5, 121.2, 107.1, 105.2, 71.5, 60.1, 34.2, 26.3, 9.8 ppm. IR (KBr): ν_{max} 3405, 2509, 2075, 1690, 1438, 1353, 1119, 974 cm^{-1}. HR-MS (ESI, *m/z*) calcd for $C_{13}H_{14}O_5Na$ ($M+Na^+$) 273.0739; found 273.0736.

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8. Data for compound (**19**): ^1H NMR (300 MHz, $CDCl_3$) δ 6.23 (1H, s), 4.65 (2H, s), 3.97 (2H, t, $J=6.9$ Hz), 3.09 (1H, d, $J=16.5$ Hz), 2.68 (1H, d, $J=16.5$ Hz), 2.15–1.82 (4H, m), 2.00 (3H, s), 0.98 (9H, s), 0.97 (9H, s), 0.17 (6H, s), 0.15 (6H, s) ppm.
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11. The *O*,*O*′-dimethyl derivative of (±)-terreinol was also synthesized by a similar way. However, the final deprotections were unsuccessful by using a variety of conditions.