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Synthesis of (2*RS*,8*R*,10*R*)-YM-193221 and an Improved Approach to Tyroscherin, Bioactive Natural Compounds from *Pseudallescheria* sp.

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Short-step syntheses of (2*RS*,8*R*,10*R*)-YM-193221 (1) and tyroscherin (2), which are biologically active compounds isolated from *Pseudallescheria* sp., were accomplished in six and eight steps from L-tyrosine. The relative stereochemistry of natural YM-193221 was determined to be 8*R,10*R**.**

Key words: YM-193221; tyroscherin; total synthesis

Hayakawa *et al.* isolated tyroscherin (**2**) in 2004 from the mycelia of *Pseudallescheria* sp. as a selective growth inhibitor of IGF-1-dependent MCF-7 cells.[1)] Its analogous compound, YM-193221 (**1**), was also isolated by Kamigiri *et al.* in the same year from the fermentation broth of *Pseudallescheria elipsoidea* as an antifungal antibiotic.[2)] Both compounds contain a 2-amino-1-(4-hydroxyphenyl)-8,10-dimethylundec-6-ene framework with a hydroxy- or oxo-group at the C3 position. We started the syntheses of these compounds with the objective of further research into their bioactivity and structure-activity relationship. We have already reported our previous studies to revise the stereochemistry of tyroscherin by enantioselective syntheses of its stereoisomers, and to evaluate the biological activities.[3,4)] Maier *et al.* have also recently reported the synthesis of tyroscherin by using asymmetric aldol condensation and Curtius rearrangement as the key steps.[5)] We report here the short-step synthesis of (2*RS*,8*R*,10*R*)-YM-193221 (**1**) and the second-generation synthesis of tyroscherin (**2**).

Results and Discussion

*Synthesis of (*2RS*,8*R*,10*R*)-YM-193221 (1)*

The structure of YM-193221 had been proposed as **1** from the results of a spectroscopic analysis, but the stereochemistry at the three chiral centers remained unknown.[2)] Since YM-193221 and tyroscherin are similar in their structural features and biological origins, we assumed that the stereochemistry of both compounds would be the same.[1,3,4)] In addition, Organ *et al.* have reported the difference in ^{13}C-NMR chemical shifts between the diastereomeric 3,5-dimethylhept-1-enyl chains,[6)] and the quoted chemical shifts of natural YM-193221 ($\delta_{C8\text{–}Me} = 21.6$, $\delta_{C10\text{–}Me} = 19.0$, and $\delta_{C11} = 29.9$) were in good accordance with those of their *syn* compounds. We therefore presumed the absolute configuration of YM-193221 to be 2*S*,8*R*,10*R* and commenced its synthesis.

In order to synthesize the (2*S*,8*R*,10*R*)-isomer (**1**) most efficiently, we constructed the C-C bond between C3 and C4 at a late stage of the synthesis. We did this by selecting the coupling reaction of Weinreb amide **9** and an organolithium reagent which could be generated from iodide **6**. The synthesis of **1** is shown in Scheme 1. Enantiomerically pure aldehyde **3**[6)] was subjected to a Wittig reaction with 3-hydroxypropyltriphenylphosphonium bromide (**4**). Although the Wittig reaction under the usual conditions afforded an inseparable 1:1 mixture of desired (*E*)- and undesired (*Z*)-olefins, Schlosser's conditions[7)] selectively gave (*E*)-olefin **5** *via* a trianion intermediate in a moderate yield. Treating alcohol **5** with I_2 and PPh_3 afforded iodide **6**, one of the coupling units, in a good yield. On the other hand, L-tyrosine was converted to the corresponding methyl ester, and subsequent reductive dimethylation of the amino group with aqueous formaldehyde and Pd–C afforded **7**. After protecting the phenolic hydroxy group with a TBS group, resulting silyl ether was treated with MeNHOMe·HCl and *i*-PrMgBr to give Weinreb amide **9**. This amide was reacted with an organo-lithium reagent generated from iodide **6** to give desired ketone **10** in a 34% yield (66% based on recovered **9**). However, the C2 position of **10** was prone to epimerization, and amino-ketone **10** was obtained only as an inseparable 1:1 mixture of diastereomers at C2 under any reaction conditions. The total synthesis of (2*RS*,8*R*,10*R*)-YM-193221 (**1**) was accomplished after deprotection in a 48% yield over six steps.[8)] The relative stereochemistry of the natural product was clearly indicated to be 8,10-*syn*, as we expected, by the similarity of spectroscopic data between the synthesized mixture and the natural product.[2)] However, the differences between both synthesized diastereomers in their ^{1}H- and ^{13}C-NMR spectral data ($\delta_{H2} = 3.33$ and 3.34 ppm, $\delta_{H7} = 5.15$ and 5.17 ppm, and $\delta_{C4} = 42.6$ and 42.7 ppm) were too small and prevented us from providing any further information about the stereochemistry of the natural product. Reisolation of the natural product would be

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Abbreviations: IGF, insulin-like growth factor; TBS, *tert*-butyldimethylsilyl; DMF, *N*,*N*-dimethylformamide; THF, tetrahydrofuran; DIBAL, diisobutylaluminum hydride; TFA, trifluoroacetic acid; MOM, methoxymethyl; Boc, *tert*-butoxycarbonyl

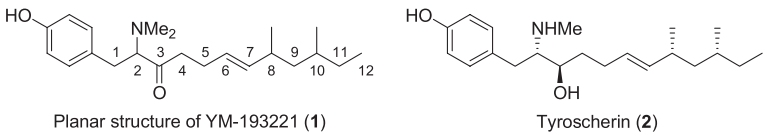
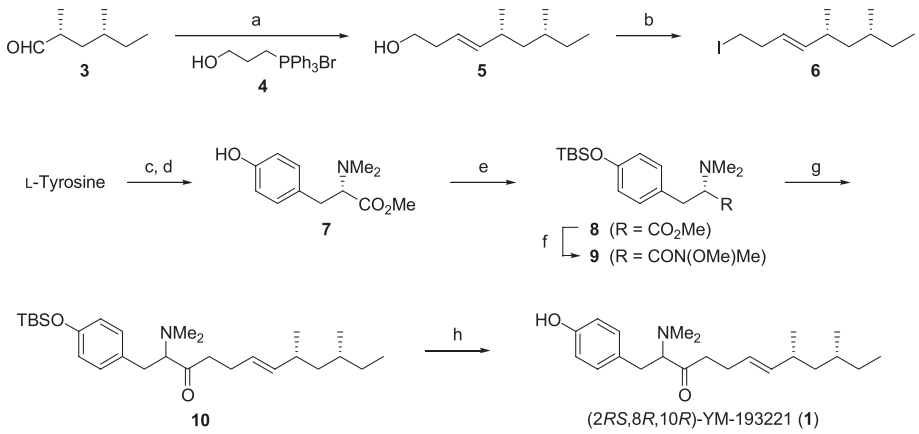
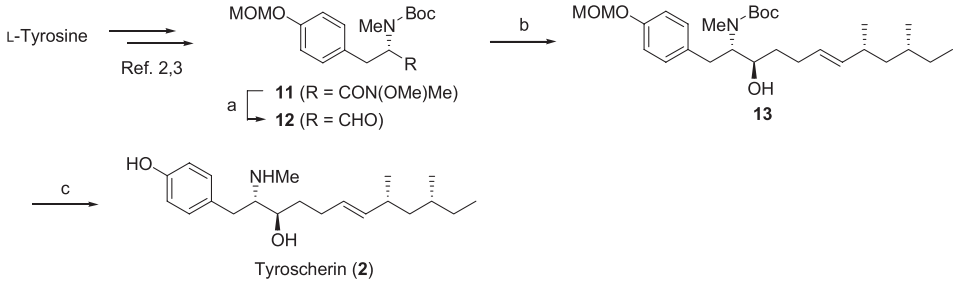


Fig. 1. Structures of YM-193221 (**1**) and Tyroscherin (**2**).



Scheme 1. Synthesis of (2*RS*,8*R*,10*R*)-YM-193221 (**1**).
Reagents: (a) **4**, PhLi, LiBr then **3**, PhLi then *t*-BuOH, *t*-BuOK, THF, 47%, (*E*)-only; (b) I_2, PPh_3, imidazole, CH_2Cl_2, 84%; (c) $SOCl_2$, MeOH; (d) H_2, Pd–C, aq. HCHO, MeOH, 89% in 2 steps; (e) TBSCl, imidazole, DMF, 97%; (f) MeNHOMe·HCl, *i*-PrMgBr, THF, 92%; (g) **6**, *t*-BuLi, ether, then **9**, 36%, 66% based on recovered **9**; (h) conc. HCl, MeOH, THF, 91%.



Scheme 2. Synthesis of Tyroscherin (**2**).
Reagents: (a) DIBAL, ether; (b) **6**, *t*-BuLi, ether, then **12**, 32% (single diastereomer), 54% based on recovered **12**; (c) TFA, MeOH, THF, H_2O, quant.

necessary to determine the stereochemistry at the C2 position.

Synthesis of tyroscherin (2)

Having succeeded in the short-step synthesis of **1**, our next objective was an improved short-step synthesis of antitumorial tyroscherin (**2**) by using a similar approach. The synthesis of **2** is shown in Scheme 2. Weinreb amide **11**,[3,4] which had been prepared from L-tyrosine in an 82% yield over five steps, was subjected to reduction in the same manner as already reported to give aldehyde **12**. This was stereoselectively reacted under Felkin-Anh control with 5,6-dimethylnon-3-enyllithium to give 2,3-*anti*-amino alcohol **13** in a 32% yield (54% based on recovered **12**) in two steps. After deprotecting with trifluoroacetic acid and recrystallization, the short-step synthesis of tyroscherin was achieved in a 32% yield over eight steps from L-tyrosine. The overall yield and number of steps were improved from our previous synthesis of tyroscherin (19% over 13 steps).

In summary, we succeeded in the first total synthesis of (2*RS*,8*R*,10*R*)-YM-193221 (**1**) in a 48% yield over six steps and determined its relative stereochemistry to be 8,10-*syn*. We also achieved an improved short-step synthesis of tyroscherin (**2**) in eight steps and 32% overall yield which is five steps less than required for our previous synthesis. Our work is still underway to determine the absolute configuration of natural YM-193221 by improving some steps in the synthesis.

Experimental

Optical rotation data were recorded with a Jasco P-2100 polarimeter, IR spectra were measured with a Jasco FT/IR-4100 spectrophotometer, and ^{1}H- and ^{13}C-NMR data were recorded with a Jeol JNM ECS400 spectrometer. Chemical shift (δ) data are referenced to the residual solvent peak of the internal standard ($CDCl_3$: $\delta_H = 7.26$, $\delta_c = 77.0$; CD_3OD: $\delta_H = 3.30$, $\delta_C = 49.0$). Mass spectra were recorded with a Jeol JMS SX102 instrument. Column chromatography was performed with Wakogel C-200 (0.075–0.150 mm) or Wakogel FC-40 (0.020–0.040 mm).

(3E,5R,7R)-5,7-Dimethylnon-3-en-1-ol (5). To a mixture of anhydrous lithium bromide (487 mg, 5.61 mmol), 3-hydroxypropyltriphenylphosphonium bromide (1.07 g, 2.67 mmol) and THF (35 ml) was

added a solution of phenyllithium in ether/cyclohexane (*ca.* 3/1, 1.15 M, 4.76 ml, 5.47 mmol) at −78 °C under an argon atmosphere. The reaction mixture was stirred for 15 min at the same temperature and for a further 15 min at room temperature. After cooling to −78 °C, to the resulting orange mixture were successively added dropwise a solution of aldehyde **3** (342 mg, 2.67 mmol) in THF (2 ml) and a solution of phenyllithium (1.15 M, 2.43 ml, 2.79 mmol). The reaction mixture was stirred for 15 min at −78 °C and then for 15 min at room temperature. The cherry red solution was cooled to −78 °C, before successively adding a solution of *t*-BuOH (281 µl, 2.94 mmol) in THF (3 ml) and *t*-BuOK (360 mg, 3.21 mmol). After stirring for 15 min at room temperature, the reaction mixture was poured into a saturated aqueous ammonium chloride solution and extracted with ethyl acetate. The organic layer was successively washed with water and brine, and dried over anhydrous magnesium sulfate. After concentrating *in vacuo*, the residue was subjected to flash chromatography over silica gel. Elution with hexane/ethyl acetate (20:1) gave **4** (212 mg, 47%) as a colorless oil. $[\alpha]_D^{24}$ −29 (*c* 1.0, $CHCl_3$). IR (film) ν cm^{-1}: 3340, 2960, 1462, 1242, 1048. ^{1}H-NMR (400 MHz, CD_3OD) δ: 0.83 (3H, d, J = 6.4 Hz), 0.86 (3H, t, J = 7.5 Hz), 0.94 (3H, d, J = 6.8 Hz), 1.00 (1H, ddd, J = 13.5, 9.0, 5.0 Hz), 1.06–1.40 (4H, m), 2.12–2.37 (3H, m), 3.53 (2H, t, J = 7.8 Hz), 5.28 (1H, dd, J = 15.1, 7.3 Hz), 5.38 (1H, dt, J = 15.1, 6.7 Hz). ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 11.3, 19.0, 21.7, 29.9, 31.9, 34.5, 36.0, 44.2, 62.0, 123.8, 140.5. *Anal.* Found: C, 77.51; H, 12.73%. Calcd. for $C_{11}H_{22}O$: C, 77.58; H, 13.02%.

*(3*E*,5*R*,7*R*)-1-Iodo-5,7-dimethylnon-3-ene (**6**).* To a mixture of alcohol **5** (121 mg, 0.71 mmol), triphenylphosphine (281 mg, 1.07 mmol), imidazole (111 mg, 1.63 mmol) and CH_2Cl_2 (10 ml) were added iodine beads (272 mg, 1.07 mmol) portionwise at 0 °C. After stirring for 2.5 h at room temperature, MeOH (1 ml) was added to the reaction mixture, and the mixture was concentrated *in vacuo*. The residue was subjected to flash chromatography over silica gel. Elution with hexane gave **6** (167 mg, 84%) as a colorless oil. $[\alpha]_D^{25}$ −24 (*c* 1.0, $CHCl_3$). IR (film) ν cm^{-1}: 2959, 1457, 1241, 1168. ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 0.82 (3H, d, J = 6.4 Hz), 0.85 (3H, t, J = 6.4 Hz), 0.95 (3H, d, J = 6.8 Hz), 1.01 (1H, ddd, J = 13.6, 9.2, 5.2 Hz), 1.14 (1H, m), 1.18–1.43 (3H, m), 2.19 (1H, m), 2.50–2.57 (2H, m), 3.10–3.19 (2H, m), 5.22–5.39 (2H, m). ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 6.4, 11.3, 18.9, 21.6, 30.0, 31.8, 34.4, 36.7, 44.1, 126.5, 139.5. *Anal.* Found: C, 46.97; H, 7.33%. Calcd. for $C_{11}H_{21}I$: C, 47.15; H, 7.55%.

*Methyl (*R*)-*N,N*-dimethyltyrosinate (**7**).* To a mixture of L-tyrosine (6.04 g, 33.1 mmol) and MeOH (21 ml) was added thionyl chloride (2.67 ml, 12.6 mmol) at 0 °C. The reaction mixture was refluxed for 4 h and then concentrated *in vacuo*. The crude colorless solid (7.72 g) was used for the next reaction without further purification. A mixture of the crude solid (3.90 g), 10% Pd–C (1.0 g), a 47% aqueous formaldehyde solution (5.65 ml, 69.7 mmol) and MeOH (75 ml) was stirred vigorously for 3 h under a hydrogen atmosphere. The mixture was then filtered through Celite® and concentrated *in vacuo*. To the resulting residue was added a 10% aqueous sodium bicarbonate solution, and the mixture extracted with ethyl acetate. The organic layer was successively washed with water and brine, dried over anhydrous magnesium sulfate and concentrated *in vacuo*. The residue was subjected to chromatography over silica gel. Elution with $CHCl_3$/MeOH (20:1) gave **7** (3.35 g, 89% in 2 steps) as a white solid. Mp 124–128 °C. $[\alpha]_D^{27}$ +31 (*c* 1.0, $CHCl_3$). IR (nujol) ν cm^{-1}: 2923, 2853, 2672, 1730, 1465, 1250. ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 2.43 (6H, s), 2.88–3.10 (2H, m), 3.44 (1H, m), 3.61 (3H, s), 6.70 (2H, d, J = 8.3 Hz), 7.03 (2H, d, J = 8.3 Hz). *Anal.* Found: C, 64.95; H, 7.57; N, 6.43%. Calcd. for $C_{12}H_{17}NO_3$: C, 64.55; H, 7.67; N, 6.27%. The other physical properties were identical to those reported.[9)]

*Methyl (*R*)-*N,N*-dimethyl-*O*-(*tert*-butyldimethylsilyl)tyrosinate (**8**).* To a solution of phenol **7** (2.23 g, 10.0 mmol) in DMF (50 ml) were added imidazole (1.09 g, 16.0 mmol) and TBSCl (2.26 g, 15.0 mmol) at 0 °C. The reaction mixture was stirred for 18 h, diluted with ether, and poured into a saturated aqueous sodium bicarbonate solution. The mixture was extracted with ether, and successively washed with water and brine. The organic layer was dried over anhydrous magnesium sulfate and concentrated *in vacuo*. The resulting residue was subjected to chromatography over silica gel. Elution with $CHCl_3$/MeOH (25:1) gave **8** (3.26 g, 97%) as a colorless oil. $[\alpha]_D^{27}$ +30 (*c* 1.0, MeOH). IR (film) ν cm^{-1}: 2953, 1735, 1605, 1510, 1261, 1168. ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 0.17 (6H, s), 0.96 (9H, s), 2.37 (6H, s), 2.87 (1H, dd, J = 13.1, 5.6 Hz), 2.97 (1H, dd, J = 13.1, 9.9 Hz), 3.35 (1H, dd, J = 9.9, 5.6 Hz), 3.57 (3H, s), 6.74 (2H, d, J = 8.4 Hz), 7.03 (2H, d, J = 8.4 Hz). ESI-TOFMS m/z: calcd. for $C_{18}H_{31}NNaO_3Si^+$ $[M + Na]^+$, 360.1965; found, 360.1953.

*(*R*)-3-[4-(*tert*-Butyldimethylsilyloxy)phenyl]-2-(*N,N*-dimethylamino)-*N*-methoxy-*N*-methylpropanamide (**9**).* To a mixture of ester **8** (1.62 g, 4.80 mmol) and *N*,*O*-dimethylhydroxylamine hydrochloride (936 mg, 9.60 mmol) in THF (50 ml) was added a solution of isopropylmagnesium bromide in THF (0.67 M, 28.7 ml, 19.2 mmol) at −20 °C. After stirring for 1 h at the same temperature, the reaction mixture was warmed to room temperature, poured into a saturated aqueous ammonium chloride solution and extracted with ethyl acetate. The organic layer was successively washed with water and brine, dried over anhydrous magnesium sulfate and concentrated *in vacuo*. The residue was subjected to chromatography over silica gel. Elution with $CHCl_3$/MeOH (30:1) gave **9** (1.61 g, 92%) as a colorless oil. $[\alpha]_D^{24}$ +29.7 (*c* 1.0, $CDCl_3$). IR (film) ν cm^{-1}: 2933, 1660, 1510, 1260, 1171. ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 0.14 (6H, s), 0.96 (9H, s), 2.40 (6H, s), 2.79 (1H, dd, J = 12.8, 3.6 Hz), 3.08 (3H, s), 3.11 (1H, m), 3.15 (3H, s), 3.86 (1H, m), 6.72 (2H, d, J = 8.4 Hz), 7.06 (2H, d, J = 8.4 Hz). ESI-TOFMS m/z: calcd. for $C_{19}H_{34}N_2NaO_3Si^+$ $[M + Na]^+$, 389.2231; found, 389.2259.

*(2*RS*,6*E*,8*R*,10*R*)-1-[4-(*tert*-Butyldimethylsilyloxy)phenyl]-2-(*N,N*-dimethylamino)-8,10-dimethyldodec-6-en-3-one (**10**).* Under an argon atmosphere, to a solution of iodide **6** (60 mg, 0.21 mmol) in ether (1 ml) was added a solution of *tert*-butyl-lithium in pentane (1.76 M, 286 µl, 0.50 mmol) at −78 °C, and the reaction mixture was stirred for 15 min at the same temperature. The resulting solution of the lithium reagent was added slowly to a solution of Weinreb amide **9** (78 mg, 0.21 mmol) in ether (1 ml) at −78 °C. The reaction mixture was then allowed to warm to room temperature. After stirring for 1 h, the reaction mixture was poured into a saturated ammonium chloride solution and extracted with ethyl acetate. The organic layer was successivelywashed with 1 N HCl, a saturated sodium bicarbonate solution and brine, and dried over anhydrous magnesium sulfate. After concentrating, the resulting residue was chromatographed over silica gel. Elution with toluene/acetone (20:1) gave **10** (35 mg, 36%, 66% based on recovery) as a colorless oil and recovered **9** (36 mg). $[\alpha]_D^{22}$ −14 (*c* 1.0, $CHCl_3$). IR (film) ν cm^{-1}: 2958, 1715, 1607, 1509, 1261. ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 0.16 (6H, s), 0.78 [3H, dd, J = 6.8, 1.2 ($J_{10\text{-Me-H9a}}$) Hz], 0.83 (3H, t, J = 7.2 Hz), 0.88 (3H, d, J = 6.8 Hz), 0.95 (1H, m), 0.96 (9H, s), 1.00–1.29 (4H, m), 1.97–2.23 (4H, m), 2.34 (6H, s), 2.49 (1H, m), 2.77 (1H, dd, J = 13.2, 4.0 Hz), 2.92 (1H, dd, J = 13.2, 10.0 Hz), 3.33 (1H, dd, J = 10.0, 4.0 Hz), 5.15 (0.5H, dd, J = 15.2, 7.2 Hz), 5.16 (0.5H, dd, J = 15.2, 6.7 Hz), 5.21 (1H, dt, J = 15.2, 6.0 Hz), 6.72 (2H, d, J = 8.4 Hz), 7.00 (2H, d, J = 8.4 Hz). ^{13}C-NMR (100 MHz, $CDCl_3$) δ: −4.5, 11.3, 18.2, 18.9, 21.7, 25.7, 26.3 (0.5, C5), 26.3 (0.5, C5), 29.9 (0.5, C11), 29.9 (0.5, C11), 30.7 (0.5, C1), 30.7 (0.5, C1), 31.7, 34.2, 42.1, 42.8 (0.5, C4), 42.9 (0.5, C4), 44.3, 76.7, 120.0, 126.6, 130.2, 131.5, 137.2, 153.9, 210.4. ESI-TOFMS m/z: calcd. for $C_{28}H_{49}NNaO_2Si^+$ $[M + Na]^+$, 482.3425; found, 482.3420.

*(2*RS*,6*E*,8*R*,10*R*)-2-(*N,N*-Dimethylamino)-1-(4-hydroxyphenyl)-8,10-dimethyldodec-6-en-3-one [**1**, (2*RS*,6*E*,8*R*,10*R*)-YM-193221].* To a mixture of silyl ether **10** (19 mg, 0.041 mmol), THF (1 ml) and MeOH (1 ml) was added conc. HCl (200 µl), and the reaction mixture was stirred for 48 h at room temperature. The reaction mixture was then concentrated *in vacuo* at 40 °C. The resulting residue was subjected to flash chromatography over silica gel. Elution with CH_2Cl_2/acetone/isopropylamine (350:50:1) gave **1** (13 mg, 91%) as a slightly yellow oil. $[\alpha]_D^{27}$ −16 (*c* 1.0, $CHCl_3$). IR (film) ν cm^{-1}: 3363, 2959, 1714, 1614, 1516, 1456, 1247. ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 0.78 [3H, dd, J = 6.4, 1.2 ($J_{10\text{-Me-H9a}}$) Hz], 0.83 (3H, t, J = 7.2 Hz), 0.88 (3H, d, J = 6.8 Hz), 0.95 (1H, ddd, J = 13.6, 8.8, 5.2 Hz), 1.09 (1H, m), 1.13–1.35 (3H, m), 2.02–2.27 (4H, m), 2.34 (6H, s), 2.53 (1H, m), 2.77 (1H, dd, J = 13.6, 4.4 Hz), 2.92 (1H, dd, J = 13.6, 9.6 Hz), 3.33 (0.5H, dd, J = 9.6, 4.4 Hz), 3.34 (0.5H, dd, J = 9.6, 4.4 Hz), 5.15 (0.5H, dd, J = 15.6, 7.6 Hz), 5.17 (0.5H, dd, J = 15.6, 7.2 Hz), 5.22 (1H, dt,

$J = 15.6$, 5.6 Hz), 6.71 (2H, d, $J = 8.4$ Hz), 7.00 (2H, d, $J = 8.4$ Hz). ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 11.3, 19.0, 21.7, 26.3, 29.9, 30.6, 31.7, 34.2, 42.1, 42.6 (0.5, C4), 42.7 (0.5, C4), 44.3, 74.7, 115.3, 126.5, 130.3, 130.7, 137.2, 154.1, 210.6. ESI-TOFMS m/z: calcd. for $C_{22}H_{36}NO_2^+$ $[M + H]^+$, 346.2741; found, 346.2782.

tert-*Butyl (1*S*,2*R*,5*E*,7*R*,9*R*)-[1-[4-(methoxymethoxy)benzyl]-2-hydroxy-7,9-dimethylundec-5-enyl]methylcarbamate (**13**).* Aldehyde **12** was synthesized from Weinreb amide **11** (382 mg, 1.00 mmol) in the same manner as that reported[3,4] to give crude aldehyde **12** (323 mg) as a colorless oil. Under an argon atmosphere, to a solution of iodide **6** (98 mg, 0.35 mmol) in ether (2 ml) was added a solution of *tert*-butyllithium in pentane (1.76 M, 286 µl, 0.50 mmol) at $-78\,^\circ$C, and the mixture was stirred for 30 min at the same temperature. The resulting solution of the lithium reagent was slowly added to a solution of crude aldehyde **12** (113 mg, 0.349 mmol) in ether (1 ml) at $-78\,^\circ$C. The reaction mixture was then allowed to warm to room temperature. After stirring for 1 h, the reaction mixture was poured into a saturated ammonium chloride solution and extracted with ethyl acetate. The organic layer was successively washed with 1 N HCl, a saturated sodium bicarbonate solution and brine, and dried over anhydrous magnesium sulfate. After concentrating *in vacuo*, the residue was subjected to flash chromatography over silica gel. Elution with CH_2Cl_2/acetone/isopropylamine (500:25:1) gave **13** (57 mg, 32%, 54% based on recovery) as a colorless oil and recovered **12** (26 mg, 29%). $[\alpha]_D^{22}$ -46.3 (c 1.35, $CHCl_3$). IR (film) ν cm^{-1}: 3435, 2961, 1669, 1511, 1154. ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 0.82 (3H, d, $J = 7.4$ Hz), 0.84 (3H, t, $J = 7.3$ Hz), 0.93 (3H, d, $J = 7.1$ Hz), 0.90–1.70 (7H, m), 1.40 (9H, s), 2.02–2.25 (3H, m), 2.49 (1.5H, s), 2.68 (1.5H, s), 2.90 (0.5H, m), 3.00–3.17 (1.5H, m), 3.44 (1.5H, s), 3.47 (1.5H, s), 3.50–3.91 (2H, m), 5.14 (2H, s), 5.15–5.45 (2H, m), 6.94 (2H, d, $J = 8.7$ Hz), 7.06 (1H, d, $J = 8.7$ Hz), 7.08 (1H, d, $J = 8.7$ Hz). ESI-TOFMS m/z: calcd. for $C_{28}H_{47}N_2NNaO_5$ $[M + Na]^+$, 500.3346; found, 500.3356.

*(2*S*,3*R*,6*E*,8*R*,10*R*)-1-(4-Hydroxyphenyl)-8,10-dimethyl-2-(methylamino)undec-6-en-3-ol (**2**, tyroscherin).* To a mixture of silyl ether **13** (20 mg, 0.042 mmol), MeOH (2 ml), THF (1 ml) and water (1 ml) was added trifluoroacetic acid (300 µl), and the mixture was stirred for 4 h at room temperature. The reaction mixture was then concentrated *in vacuo* at 60 °C. The resulting residue was subjected to flash chromatography over silica gel. Elution with $CHCl_3$/MeOH (7:1) and subsequent recrystallization from hexane/ether gave **2** (14 mg, quant.) as colorless needles. Mp 122–126 °C. $[\alpha]_D^{25}$ -21 (c 0.35, MeOH). IR (KBr) ν cm^{-1}: 3239, 2961, 1671, 1203, 1185, 1146. ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 0.83 (3H, d, $J = 6.4$ Hz), 0.85 (3H, t, $J = 7.6$ Hz), 0.91 (3H, d, $J = 6.4$ Hz), 0.99 (1H, ddd, $J = 13.2$, 8.8, 4.2 Hz), 1.13 (1H, m), 1.17–1.38 (3H, m), 1.43–1.61 (2H, m), 2.00 (1H, m), 2.10–2.25 (2H, m), 2.61 (3H, s), 2.86 (1H, dd, $J = 14.4$, 8.0 Hz), 2.90 (1H, dd, $J = 14.4$, 6.8 Hz), 3.34 (1H, m), 3.83 (1H, ddd, $J = 9.2$, 3.2, 3.2 Hz), 5.23 (1H, dd, $J = 15.2$, 8.4 Hz), 5.33 (1H, dt, $J = 15.2$, 6.4 Hz), 6.77 (2H, quasi d, $J = 8.8$ Hz), 7.10 (2H, quasi d, $J = 8.8$ Hz). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 11.7, 19.4, 22.3, 29.9, 31.1, 32.4, 33.1, 33.2, 35.8, 45.6, 66.8, 68.7, 116.9, 127.6, 128.4, 131.3, 138.8, 158.0. ESI-TOFMS m/z: calcd. for $C_{21}H_{36}NO_2^+$ $[M + H]^+$, 334.2741; found, 334.2719. The physical properties of **2** were identical to those reported.[1,3,4]

References and Notes

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8) Alternatively, oxidation of *N*-methyltyroscherin (**14**), prepared from tyroscherin (aq. HCHO, $NaBH_3CN$, CH_3CN, 94%), by several reagents (PCC, Dess-Martin periodinane) resulted in decomposition of the starting material. Oxidation of **14** was succeeded by using TPAP, NMO, but the corresponding YM-193221 (**1**) was also given as a 1:1 mixture of diastereomers at C2.
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