

Synthesis of tavacpalescensin and occidol *via* a common intermediate

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The symmetrical benzosuberone **3** has been used in the synthesis of tavacpalescensin by an Emmons–Wadsworth condensation, selenium dioxide oxidation and diisobutylaluminium hydride reduction. For the elaboration of occidol, α -diazotization, Wolff rearrangement and reaction with methyllithium were involved.

Introduction

Sponges of the *Dysidea* genus, particularly *D. pallelescens*, elaborates many sesquiterpenoid metabolites, among them pallelescensin-1,¹ pallelescensin-2,¹ dihydropallelescensin-2 (pentan-pallelescensin),² pallelescensin-A,³ pallelescensin-B,³ pallelescensin-C,³ pallelescensin-D,³ pallelescensin-E,⁴ pallelescensin-F,⁴ pallelescensin-G,⁴ and tavacpalescensin (**1**)⁵ possess a furan nucleus. These compounds have attracted considerable synthetic attention^{6–17} because some of them possess unique structures and physiological activities. For example, there is evidence that nudibranch molluscs obtain such substances from their dietary sponges and concentrate them in their skin glands for defense against predators.¹⁸ Our interest in the synthesis of tavacpalescensin which was isolated from *D. avara* (specimen contaminated with *Pleraplysilla spinifera*) stemmed from (1) the fact that no report of such an endeavor is known, (2) its structural similarity to the monocyclic sesquiterpene **2** from the marine alga *Laurencia nidifica* which has been obtained by us previously,¹⁹ although biogenetically these two compounds are derived from divergent pathways, (3) our related activities in the synthesis of *D. herbaceae* constituents such as furodysin,²⁰ furodysinin,²¹ and herbasolide,²² and, perhaps most importantly, (4) our recent focus on exploiting symmetry aspects in molecular construction.²³ In accessing certain compounds an approach that passes through a series of symmetrical precursors limits the generation of regio- and/or stereoisomers, thereby the effort is facilitated. At an appropriate moment the advanced symmetrical intermediates are desymmetrized in verging towards the targets.

We identified a symmetrical dimethylbenzosuberone **3** as the key intermediate in a route to tavacpalescensin. This compound should be available from some simple symmetrical aromatic compounds. Furthermore, we envisioned that the dimethylbenzosuberone would be of utility for the preparation of occidol (**4**).

Occidol is a sesquiterpene alcohol constituent of *Thuja occidentalis* L.²⁴ Because of its relatively simple structure occidol has been synthesized by a variety of methods.^{25–33} Our two previous publications^{28,29} in this area have already shown the potential of symmetry considerations. However, we felt that the synthesis of **1** is also worthy of examination.

Results and discussion

Our method of employing a common intermediate for the synthesis of tavacpalescensin and occidol started from α^2, α^3 -dibromoprehnetene (**5**).³⁴ The initial attempt at forming a seven-membered ring by alkylation of the dianion of methyl

acetoacetate³⁵ was prompted by the fear of an apparently more favorable cyclopentane ring being formed using a stabilized carbanion. The unsatisfactory results led us to change the nucleophile to dimethyl acetonedicarboxylate. The mixture of products (ketone + enol forms) was directly hydrolyzed and decarboxylated to provide the desired benzosuberone **3** in 46% yield.

To begin annexation of the furan moiety we submitted **3** to an Emmons–Wadsworth condensation. The conjugated ester **6** was generated in 93% yield. Interestingly, the desymmetrization affected the most remote sites as revealed by both proton and carbon NMR spectra. Formation of the butenolide **7** was accomplished in 67% yield by heating the ester with selenium dioxide in glacial acetic acid. The last step of the synthesis was a lactone reduction with diisobutylaluminium hydride in tetrahydrofuran under nitrogen at -20°C . Tavacpalescensin was obtained (97% yield).

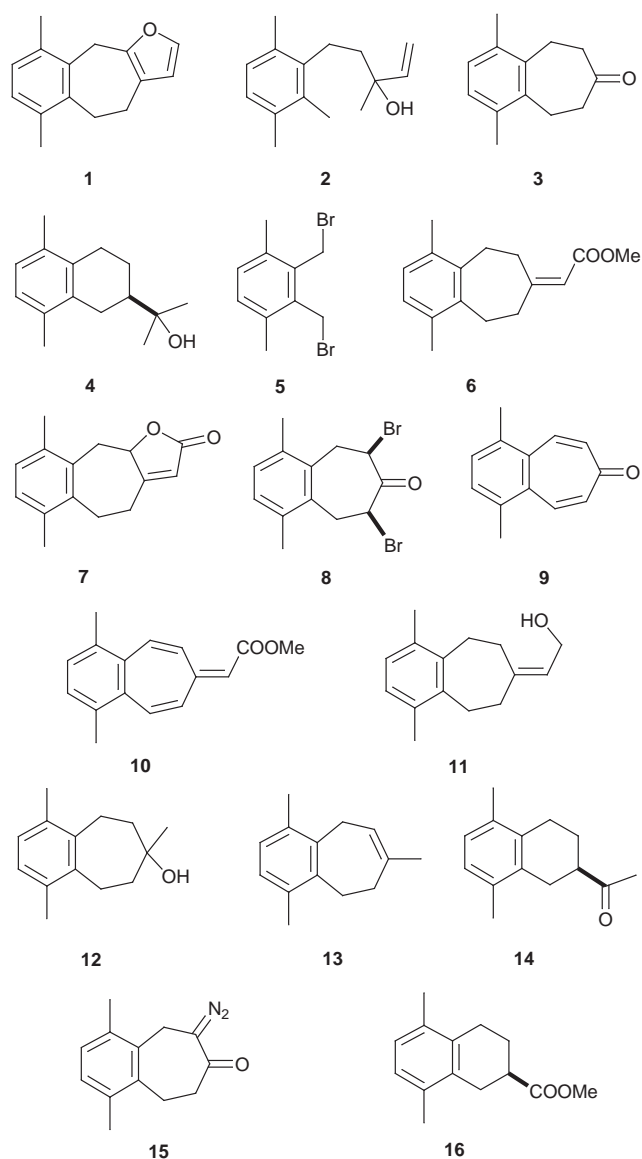
We have also studied some other routes to tavacpalescensin. Bromination of **3** in acetic acid produced in 91% yield a symmetrical α, α' -dibromide (**8**) which underwent twofold dehydrobromination on treatment with $\text{LiBr} \cdot \text{Li}_2\text{CO}_3$. However, we were not able to convert the benzotropone **9** into the benzoheptafulvene ester **10** either by an Emmons–Wadsworth condensation directly or by a Reformatsky reaction on the corresponding *O*-ethylbenzotropenium tetrafluoroborate which was obtained by reacting **9** with Meerwein's salt.

Before we found the satisfactory conditions for the direct transformation of **6** into **7**, we also attempted to effect a cyclization of the allylic alcohol **11** with lead(IV) acetate. The alcohol was readily obtained from **6** by lithium aluminium hydride reduction in 86% yield. However, the oxidative cyclization³⁶ failed to deliver the desired dihydrofuran product.

Another reason for our bromination experiment was to induce a ring contraction of the bromoketone by the Favorskii rearrangement. However, the exposure of **8** to sodium methoxide in methanol led to the benzotropone **9** only. Since the monobromide of **3** could not be procured in a pure form with acceptable yield, this approach to occidol was abandoned.

Ring contraction of **3** with lead(IV) acetate–boron trifluoride–diethyl ether³⁷ also failed. We then converted **3** into the tertiary alcohol **12** by reaction with methyllithium and thence into olefin **13** by thermal dehydration at 170°C . Unfortunately, a clean formation of the methyl ketone **14** from **13** could not be achieved using either thallium(III) nitrate³⁸ or by sequential reaction with *N*-bromosuccinimide and silver nitrate.

The successful experiments involved diazotization of **3** *via* hydroxymethylation and direct treatment of the sodium salt with methanesulfonyl azide.³⁹ Photolysis of the α -diazoketone



15 in methanol effected a Wolff rearrangement to give the ester **16**. The final step was the reaction of **16** with methyl lithium. Occidol was obtained by a four-staged synthesis from α^2, α^3 -dibromoprehnetene in 26% overall yield.

In conclusion, we have furnished two examples to demonstrate the effectiveness of symmetry considerations in synthesis design. Tavacpalescensin and occidol have been acquired from a readily available, symmetrical intermediate.

Experimental

Infrared spectra were recorded by using a JASCO FT/IR-200 spectrophotometer. ^1H and ^{13}C NMR spectra were obtained from a Varian Unity-300 or a Bruker DRX-300 spectrometer, using CDCl_3 as solvent. The chemical shifts are reported relative to TMS ($\delta = 0$) for δ_{H} and CDCl_3 (central line of triplet, 77.0 ppm) for δ_{C} , respectively. Coupling constants (J) are given in Hz, with the signal multiplicity indicated as: s = singlet, d = doublet, t = triplet, q = quartet, br = broad signal. EI-mass spectra were measured on a TRIO-2000 instrument and JEOL JMX-HX 110 spectrometer (HRMS). Column chromatography was performed using silica gel 60 (Merck 7734, 70–230 mesh).

1,4-Dimethyl-5,6,8,9-tetrahydro-7H-benzo[a]cyclohepten-7-one (3)

A solution of sodium methoxide (from 0.52 g of Na in 15 cm^3 MeOH) was added dropwise to a stirred mixture of 2,3-

bis(bromomethyl)-*p*-xylene (3.0 g, 10 mmol) and dimethyl acetonedicarboxylate (1.8 g, 10 mmol) at 0 °C. After the addition the mixture was warmed to room temperature and kept for 12 h, poured into 10% HCl and extracted with ether. The extracts were dried over Na_2SO_4 , concentrated *in vacuo* to give a keto diester (3.0 g) which was hydrolyzed directly by heating with acetic acid (3 cm^3) and water (2 cm^3) containing concentrated H_2SO_4 (0.4 cm^3) for 8 h. The cooled solution was basified with 10% NaOH and extracted with ether. The combined extracts were dried over Na_2SO_4 , evaporated, and chromatographed, using a 1:9 EtOAc–hexane mixture as eluent to afford the ketone **3** (0.89 g, 46% for two steps). $\nu_{\text{max}}(\text{film})/\text{cm}^{-1}$ 1703; δ_{H} 2.31 (6H, s), 2.52–2.57 (4H, AA'BB'), 2.92–2.96 (4H, AA'BB'), 6.95 (2H, s); δ_{C} 20.1 (q), 24.2 (t), 43.4 (t), 128.2 (d), 132.6 (s), 138.9 (s), 210.4 (s); m/z (EI) 188 (100), 173 (36), 160 (38), 145 (57), 131 (52); M^+ 188.1200 (188.1202 calcd for $\text{C}_{13}\text{H}_{16}\text{O}$).

Methyl 2-(1,4-dimethyl-5,6,8,9-tetrahydro-7H-benzo[a]cyclohepten-7-ylidene)acetate (6)

A solution of trimethyl phosphonoacetate (0.22 g, 1.2 mmol) in dry *N,N*-dimethylformamide (2.0 cm^3) was added to a stirred suspension of sodium hydride (0.05 g, 60% NaH in mineral oil which had been washed with hexane) in the same solvent (2.0 cm^3). When hydrogen evolution ceased, a solution of ketone **3** (0.21 g, 1.1 mmol) in dry *N,N*-dimethylformamide (2.0 cm^3) was introduced. After 1 h, the mixture was poured into water and extracted with ether. The extracts were washed with water and brine, dried over Na_2SO_4 , evaporated, and chromatographed to give the conjugated ester **6** (0.25 g, 93%). $\nu_{\text{max}}(\text{film})/\text{cm}^{-1}$ 1717; δ_{H} 2.28 (3H, s), 2.30 (3H, s), 2.35–2.39 (2H, m), 2.84–2.89 (4H, m), 2.98–3.02 (2H, m), 3.68 (3H, s), 5.63 (1H, s), 6.89 (2H, s); δ_{C} 20.5 (q), 20.54 (q), 27.7 (t), 28.5 (t), 29.9 (t), 38.7 (t), 50.8 (q), 115.0 (d), 127.8 (d), 128.0 (d), 132.6 (s), 133.0 (s), 139.8 (s), 141.0 (s), 164.3 (s), 166.8 (s); m/z (EI) 244 (100), 229 (40), 197 (49), 184 (73), 169 (65); M^+ 244.1470 (244.1464 calcd for $\text{C}_{16}\text{H}_{20}\text{O}_2$).

6,9-Dimethyl-4,5,10,10a-tetrahydro-2H-benzo[5,6]cyclohepta-[1,2-*b*]furan-2-one (7)

A mixture of ester (**6**) (0.12 g, 0.49 mmol) and freshly sublimed selenium dioxide (0.06 g, 0.54 mmol) in glacial acetic acid (6.0 cm^3) was boiled for 3 h. The cooled mixture was diluted with ether, filtered, and the filtrate was washed with aqueous sodium bicarbonate and brine. Drying and evaporation left an oil which was chromatographed, using a 3:7 EtOAc–hexane mixture as eluent to furnish the butenolide **7** (0.075 g, 67%). $\nu_{\text{max}}(\text{film})/\text{cm}^{-1}$ 1759; δ_{H} 2.31 (3H, s), 2.34–2.41 (1H, m), 2.36 (3H, s), 2.55–2.64 (1H, m), 2.79–2.83 (1H, m), 3.06–3.18 (2H, m), 3.57 (1H, dd, $J = 14.1, 3.6$ Hz), 4.64–4.67 (1H, m), 5.74 (1H, s), 6.97 (2H, s); δ_{C} 20.4 (q), 20.7 (q), 26.3 (t), 29.3 (t), 33.3 (t), 81.5 (d), 115.2 (d), 128.9 (d), 129.3 (d), 132.8 (s), 133.1 (s), 134.4 (s), 172.7 (s); m/z (EI) 228 (100), 199 (82), 197 (52), 156 (38), 115 (54); M^+ 228.1163 (228.1151 calcd for $\text{C}_{15}\text{H}_{16}\text{O}_2$).

Tavacpalescensin (1) (6,9-dimethyl-5,10-dihydro-4H-benzo[5,6]cycloheptan[1,2-*b*]furan)

A solution of the butenolide **7** (0.10 g, 0.44 mmol) in dry tetrahydrofuran (5.0 mL) was treated with diisobutylaluminium hydride (0.6 cm^3 , 1 M in hexane) at –20 °C under nitrogen. After 1 h, acetic acid was added to quench the reaction mixture which was then allowed to warm to ambient temperature. The product was isolated by dilution with water, extraction with dichloromethane, drying (Na_2SO_4), evaporation, and chromatography (eluted with hexane). Tavacpalescensin (**1**) was obtained (0.09 g, 97%). $\nu_{\text{max}}(\text{film})/\text{cm}^{-1}$ 2960, 2924, 2854, 1259, 1101, 1012; δ_{H} 2.33 (3H, s), 2.34 (3H, s), 2.61–2.65 (2H, m), 3.04–3.08 (2H, m), 4.03 (2H, s), 6.06 (1H, d, $J = 1.5$ Hz), 6.86

(1H, d, $J = 7.5$ Hz), 6.93 (1H, d, $J = 7.5$ Hz), 7.12 (1H, d, $J = 1.5$ Hz); δ_C 20.2 (q), 20.6 (q), 24.2 (t), 27.4 (t), 27.8 (t), 112.2 (d), 117.6 (s), 128.1 (d), 128.4 (d), 132.6 (s), 132.9 (s), 137.9 (s), 139.1 (d), 139.5 (s), 148.8 (s); m/z (EI) 212 (81), 197 (100), 169 (24), 128 (18), 115 (15); M^+ 212.1200 (212.1202 calcd for $C_{15}H_{16}O$).

cis-6,8-Dibromo-1,4-dimethyl-5,6,8,9-tetrahydro-7H-benzo[a]-cyclohepten-7-one (8)

A solution of bromine (1.28 cm³, 1 M in acetic acid) was added dropwise to the ketone **3** (0.12 g, 0.64 mmol) in glacial acetic acid at room temperature with magnetic stirring. After 1 h the reaction mixture was diluted with water and extracted with dichloromethane. The organic extracts were washed with water, saturated sodium bicarbonate solution, brine, and dried over Na_2SO_4 . Evaporation of the filtered extracts and chromatography of the residue (eluted with 2:8 EtOAc–hexane) afforded the dibromide **8** (0.2 g, 91%). ν_{max} (film)/cm⁻¹ 1718; δ_H 2.32 (6H, s), 3.50–3.54 (4H, m), 4.33 (1H, dd, $J = 9.6, 6.6$ Hz), 7.00 (2H, s); δ_C 20.0 (q), 35.1 (t), 46.1 (d), 96.2 (d), 130.0 (s), 135.5 (s), 198.0 (s); M^+ 343.9442, 345.9380, 347.9379 (343.9411, 345.9391, 347.9371 calcd for $C_{13}H_{14}Br_2O$).

1,4-Dimethyl-7H-benzo[a]cyclohepten-7-one (9)

The dibromide **8** (0.128 g, 0.37 mmol) was added to a stirred suspension of lithium bromide (0.193 g, 2.2 mmol) and lithium carbonate (0.164 g, 2.2 mmol) in dry *N,N*-dimethylformamide (8.0 cm³) and the mixture was heated at 120 °C for 1.5 h. On cooling the reaction mixture was poured into dilute acetic acid, and extracted with dichloromethane. The organic extracts were washed with water, brine, dried (Na_2SO_4) and concentrated *in vacuo*. The residue was recrystallized from a benzene–hexane mixture to provide **9** (mp 119–120 °C; 0.055 g, 81%). ν_{max} (film)/cm⁻¹ 1633; δ_H 2.62 (6H, s), 6.80 (2H, d, $J = 12.9$ Hz), 7.32 (2H, s), 7.78 (2H, d, $J = 12.9$ Hz); δ_C 21.9 (q), 132.6 (d), 134.4 (d), 135.2 (s), 136.3 (d), 137.8 (s), 188.2 (s); M^+ 184.0881 (184.0888 calcd for $C_{13}H_{12}O$).

1,4,7-Trimethyl-6,9-dihydro-5H-benzo[a]cycloheptene (13)

To a magnetically stirred solution of ketone **3** (0.1 g, 0.53 mmol) in anhydrous ether (5 cm³) was added methylolithium (0.46 cm³, 1.4 M in hexane) under nitrogen. The resulting mixture was then refluxed for 8 h, cooled, poured into an ice-cold saturated ammonium chloride solution, and extracted with ether. The extracts were washed with brine, dried (Na_2SO_4) and concentrated *in vacuo*. The residue was purified by silica gel chromatography (3:7 EtOAc–hexane as eluent) to afford the tertiary alcohol **12** (0.093 g, 86%) which was suitable for use in dehydration. ν_{max} (film)/cm⁻¹ 3394 (br); m/z (EI) 204 (37), 171 (100), 157 (47), 131 (19); M^+ 204.1524 (204.1515 calcd for $C_{14}H_{20}O$).

The alcohol **12** (0.22 g, 1.1 mmol) was placed in a 10 cm³ round-bottomed flask and heated at 170–180 °C for 40 min. The cooled residue was taken up in ether, dried and evaporated to give the crude olefin. Purification by silica gel chromatography (5:95 EtOAc–hexane as eluent) furnished **13** (0.18 g, 90%). δ_H 1.56 (3H, s), 2.17–2.21 (2H, m), 2.28 (3H, s), 2.30 (3H, s), 3.00–3.05 (2H, m), 3.37 (2H, d, $J = 6$ Hz), 5.52 (1H, t, $J = 6$ Hz), 6.86 (2H, q, $J = 8.7$ Hz); δ_C 20.0 (q), 20.3 (q), 25.9 (q), 26.6 (t), 27.1 (t), 33.0 (t), 120.2 (d), 127.7 (d), 131.2 (s), 132.3 (s), 136.5 (s), 139.8 (s), 141.3 (s); m/z (EI) 186 (100), 171 (94), 157 (44), 143 (31), 128 (25), 91 (23); M^+ 186.1406 (186.1409 calcd for $C_{14}H_{18}$).

1,4-Dimethyl-5,6,8,9-tetrahydro-6-diazo-7H-benzo[a]cyclohepten-7-one (15)

An ice-cooled, magnetically stirred suspension of sodium hydride (0.04 g, 60% dispersion in mineral oil, washed with hexane) in anhydrous ether (2.0 cm³) was treated with 1 drop of

absolute ethanol and then with a mixture of the ketone **3** (0.188 g, 1.0 mmol) and ethyl formate (0.074 g, 1 mmol) in ether (2.0 cm³). Stirring was continued for 3 h at 0 °C and at room temperature overnight. At this point methanesulfonyl azide (0.121 g, 1.0 mmol) in ether (3.0 cm³) was added and 2 h later the reaction was quenched with water (1.0 cm³). The organic solution was separated, washed with 10% sodium hydroxide, and combined with back-extracts (3 × 10 cm³ ether) of the alkaline solution, dried, and evaporated. The residue was chromatographed, using a 1:9 EtOAc–hexane mixture as eluent to afford the α -diazoketone **15** (0.154 g, 72%). ν_{max} (film)/cm⁻¹ 2081, 1612; δ_H 2.29 (3H, s), 2.35 (3H, s), 2.58 (2H, AA'BB'), 2.97 (2H, AA'BB'), 3.80 (2H, s), 6.95 (2H, d, $J = 7.8$ Hz), 6.97 (2H, d, $J = 7.8$ Hz); δ_C 19.7 (q), 20.1 (q), 23.8 (t), 24.4 (t), 39.3 (t), 67.1 (s), 128.5 (d), 129.1 (d), 131.9 (s), 133.0 (s), 136.4 (s), 138.7 (s), 194.5 (s); m/z (EI) 214 (3), 186 (72), 171 (30), 143 (100), 141 (36), 128 (76), 115 (30), 77 (14).

Methyl 5,8-dimethyl-1,2,3,4-tetrahydronaphthalene-2-carboxylate (16)

A solution of the diazoketone (**15**) (0.1 g, 0.47 mmol) in methanol (10 cm³) was placed in a Pyrex tube and irradiated at room temperature in a Rayonet photoreactor with 253.7 nm light for 4 h. The solvent was removed and the product was purified by silica gel chromatography (1:9 EtOAc–hexane eluent) to give the ester (**16**) (0.086 g, 84%). ν_{max} (film)/cm⁻¹ 1736; δ_H 1.72–1.83 (1H, m), 2.19 (3H, s), 2.21 (3H, s), 2.23–2.29 (1H, m), 2.61–2.71 (2H, m), 2.76–2.83 (2H, m), 2.90–2.96 (1H, m), 3.74 (3H, s), 6.89 (2H, s); δ_C 19.55 (q), 19.6 (q), 25.7 (t), 26.7 (t), 29.7 (t), 39.8 (d), 51.7 (q), 127.1 (d), 133.3 (s), 133.7 (s), 133.9 (s), 134.0 (s), 176.0 (s); m/z (EI) 218 (34), 159 (29), 158 (100), 143 (72), 128 (18), 115 (10); M^+ 218.1315 (212.1207 calcd for $C_{14}H_{18}O_2$).

Occidol (4) (2-(5,8-dimethyl-1,2,3,4-tetrahydronaphthalen-2-yl)propan-2-ol)

A solution of the methyl ester (**16**) (0.06 g, 0.28 mmol) in dry ether (2.0 cm³) was added slowly to methylolithium (1 cm³, 1.4 M in ether) at room temperature with magnetic stirring. After 5 h the reaction mixture was poured into a saturated ammonium chloride solution, extracted with ether, dried, and concentrated *in vacuo*. The solid thus obtained was recrystallized from hexane to give occidol (mp 98–100 °C, lit.²⁴ mp 101–102 °C; 0.055 g, 92%). ν_{max} (film)/cm⁻¹ 3402; δ_H 1.30 (3H, s), 1.31 (3H, s), 1.34–1.44 (1H, m), 1.64–1.74 (1H, m), 2.10–2.16 (1H, m), 2.21 (3H, s), 2.22 (3H, s), 2.34 (1H, dd, $J = 16.2, 12$ Hz), 2.51–2.63 (1H, m), 2.77–2.88 (2H, m), 6.89 (2H, s); δ_C 19.5 (q), 19.6 (q), 24.1 (t), 26.7 (t), 27.3 (q), 28.1 (t), 28.8 (t), 45.5 (d), 72.7 (s), 126.9 (d), 133.5 (s), 134.0 (s), 134.9 (s), 134.0 (s); M^+ (EI) 218.1674 (218.1671 calcd for $C_{15}H_{22}O$).

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