A Synthesis of (−)-Bursatellin

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A synthesis of (−)-bursatellin has been accomplished by an application of a new procedure for oxidation at a benzylic position with $K_2S_2O_8$ to 1-acetoxy-2(*S*)-*N*-Boc-amino-3-(4-benzyloxyphenyl) propane as a key step.

Keywords (−)-bursatellin; sea hare; *N*-Boc-tyrosine; potassium persulfate; oxidation; formylation; cyanation

(−)-Bursatellin (**1**)[1] has been isolated from the sea hare, *Bursatella* sp., as a metabolite and its synthesis has been completed by an Italian group.[2] We wish to report here an alternative synthesis of this compound using a new oxidation reaction at a benzylic position with potassium persulfate ($K_2S_2O_8$).[3]

Reduction of *N*-Boc-*O*-benzyltyrosine methyl ester (**3**), obtained from *N*-Boc-*O*-benzyltyrosine (**2**) by treatment with diazomethane, with lithium aluminum hydride (LAH) in tetrahydrofuran (THF) gave the alcohol (**4**) in 76% yield. Oxidation of its *O*-acetate (**5**) with $K_2S_2O_8$ in aqueous acetonitrile gave the cyclic carbamate (**6**) and *p*-benzyloxybenzaldehyde in 40% and 23% yields, respectively. No detectable amount of the stereoisomeric compound was isolated. This fact was consistent with the result of our preliminary investigation concerning the oxidation reaction of tyrosine derivatives with potassium persulfate.[3] Hydrolysis of the cyclic carbamate with 2% aqueous potassium hydroxide and toluene (two phases) under reflux overnight followed by *N*-formylation with ethyl formate furnished the *N*-formate (**7**) in 87% yield. Removal of the benzyl group under hydrogen in the presence of palladium on carbon gave the phenol (**8**) in quantitative yield. Treatment of **8** with dimethoxypropane in acetone in the presence of camphorsulfonic acid at room temperature afforded the acetonide (**9**) in 67% yield. The spectroscopic properties of this compound showed good agreement with the data reported by the Italian group, confirming a formal synthesis of (−)-bursatellin at this stage.

Attempts at cyanoethylation of the phenolic hydroxyl group in the acetonide (**9**) with acrylonitrile using several kinds of bases and solvents were unsuccessful, as mentioned by the Italian group. Thus, we tested a two-step procedure to introduce the cyanoethyl moiety. Heating the acetonide (**9**) with 1,2-dibromoethane and potassium carbonate in ethanol with efficient stirring overnight gave the bromide (**10**) in 75% yield. Treatment of the bromide (**10**) with sodium cyanide in dimethylsulfoxide (DMSO) or some other solvents gave rise to regeneration of the phenol (**9**) as a result of the retro-Michael fragmentation reaction due to sodium hydroxide present in commercial sodium cyanide. Eventually, we found that addition of sodium dihydrogenphosphate (NaH_2PO_4) as a buffer to the cyanation reaction mixture resulted in formation of the cyanide (**11**) in 73% yield. The proton nuclear magnetic resonance (^{1}H-NMR) spectrum of the synthetic compound exhibited good agreement with the data reported by the Italian group. Hydrolysis of the acetonide group with aqueous acetic acid gave (−)-bursatellin (**1**). Its spectroscopic properties and $[\alpha]_D$ value ($[\alpha]_D$ −8.0° (*c*=0.29, MeOH)) were also in good agreement with those of (−)-bursatellin ($[\alpha]_D$ −8.8°), indicating the accomplishment of the synthesis of **1** in 6.3% overall yield starting from *N*-Boc-*O*-benzyltyrosine (**2**).

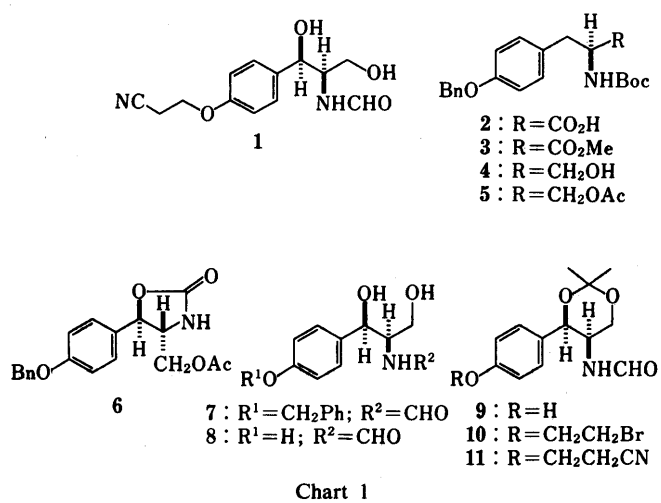

Chart 1

Experimental

Melting points were determined with a Yanagimoto micro-melting point apparatus and are uncorrected. ^{1}H-NMR spectra were recorded on Varian EM 360 (60 MHz) and JEOL FX90Q (90 MHz) spectrometers with tetramethylsilane as an internal standard. Mass spectra (MS) were recorded on a JEOL 303A spectrometer. Infrared (IR) spectra were recorded with a Shimadzu IR-408 spectrometer. Optical rotations were measured at 19—25 °C with a JASCO DIP-181 digital polarimeter. Merck Kieselgel Art. 7731 was used for flash column chromatography, and Merck Kieselgel precoated Silica gel 60 F-254 plates were used for preparative thin layer chromatography (TLC).

(2*S*)-2-*N*-Boc-amino-3-(4-benzyloxyphenyl)propanol (4) A mixture of excess ethereal diazomethane and *N*-Boc-*O*-benzyl-L-tyrosine (5.0 g, 13.5 mmol) in ether (50 ml) was kept at room temperature for a few minutes, and a few drops of acetic acid were added to the reaction mixture. The solution was washed with 2% aqueous $NaHCO_3$ and water, dried with $MgSO_4$ and evaporated. A solution of the residue in anhydrous THF (150 ml) was added dropwise to a suspension of $LiAlH_4$ (740 mg, 20.3 mmol) in anhydrous THF (150 ml) at 0 °C. The mixture was stirred for 1 h. After addition of a few drops of water to the reaction mixture, the resulting precipitates were filtered off. The filtrate was concentrated *in vacuo* to give a residue which was taken up in ether. The ethereal solution was washed with 2% aqueous HCl and water, dried with $MgSO_4$ and evaporated to dryness to give the alcohol (**4**) (3.67 g, 76%) which was recrystallized from ether–hexane as colorless needles, $[\alpha]_D$ −17.38° (*c*=1.63, MeOH), mp 102—104 °C. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3650, 3430, 1700. ^{1}H-NMR (60 MHz in $CDCl_3$) δ: 1.47 (9H, s), 2.56 (1H, br s), 2.83 (2H, d, *J*=7.2 Hz), 3.65 (2H, d, *J*=3.6 Hz), 3.54—3.94 (1H, m), 4.94 (1H, d, *J*=7.8 Hz), 5.13 (2H, s), 7.02 (2H, d, *J*=9.0 Hz), 7.28 (2H, d, *J*=9.0 Hz), 7.53 (5H, s). *Anal.* Calcd for $C_{21}H_{27}NO_4$: C, 70.56; H, 7.61; N, 3.92. Found: C, 70.37; H, 7.59; N, 3.89.

(2*S*)-2-*N*-Boc-amino-3-(4-benzyloxyphenyl)propyl Acetate (5) Acetic anhydride (6 ml) was added to a solution of the alcohol (**4**) (3.11 g, 8.72 mmol) in pyridine (30 ml). The reaction mixture was stirred at room temperature overnight, then MeOH (6 ml) was added to it. The solvent was removed *in vacuo* and the residue was extracted with ether. The organic extract was washed with 2% aqueous HCl and water, dried with $MgSO_4$ and evaporated to afford the acetate (**5**) (3.14 g, 90%), which was recrystallized from ether–hexane as white needles, $[\alpha]_D$ −6.62° (c=0.89, MeOH), mp, 95—96 °C. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3430, 1730, 1710. ^{1}H-NMR (60 MHz in $CDCl_3$) δ: 1.47 (9H, s), 2.13 (3H, s), 2.83 (2H, d, J=6.6 Hz), 3.90—4.25 (1H, m), 4.12 (2H, d, J=1.8 Hz), 4.74 (1H, d, J=7.8 Hz), 5.15 (2H, s), 7.02 (2H, d, J=9.6 Hz), 7.28 (2H, d, J=9.6 Hz), 7.57 (5H, s). *Anal.* Calcd for $C_{23}H_{29}NO_5$: C, 69.15; H, 7.32; N, 3.51. Found: C, 69.02; H, 7.12; N, 3.59.

(4*R*,5*R*)-4-Acetoxymethyl-5-(4-benzyloxyphenyl)-1,3-oxazolidine-2-one (6) Solutions of $K_2S_2O_8$ (2.26 g, 8.36 mmol) in water (30 ml) and $CuSO_4$ (134 mg, 0.84 mmol) in water (5 ml) were added successively to a solution of the acetate (**5**) (1.67 g, 4.18 mmol) in CH_3CN (35 ml) under argon. After being stirred at 110 °C (bath temperature) for 100 min, the mixture was concentrated *in vacuo*. The residue was thoroughly extracted with $CHCl_3$ and the organic layer was washed with 2% aqueous $NaHCO_3$ and water, dried with $MgSO_4$ and concentrated *in vacuo* to give a residue, which was subjected to a flash chromatography. Elution with ethyl acetate–hexane (2:3) afforded the carbamate (**6**) (567 mg, 40%) as white needles, $[\alpha]_D$ +35.21° (c=0.85, $CHCl_3$), mp, 151—154 °C. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3430, 1760, 1745. MS m/z: 341 (M^+). ^{1}H-NMR (90 MHz in $CDCl_3$) δ: 2.09 (3H, s), 3.64—4.30 (2H, m), 5.05 (2H, s), 5.29 (2H, d, J=5.4 Hz), 6.36 (1H, br s), 6.97 (2H, d, J=8.1 Hz), 7.30 (2H, d, J=8.1 Hz), 7.37 (5H, s). *Anal.* Calcd for $C_{19}H_{19}NO_5$: C, 66.85; H, 5.61; N, 4.10. Found: C, 66.68; H, 5.67; N, 4.07.

(2*R*,3*R*)-3-(4-Benzyloxyphenyl)-2-formylamino-1,3-propanediol (7) A mixture of the carbamate (**6**) (513 mg, 1.50 mmol), 3% aqueous KOH (15 ml) and toluene (15 ml) was refluxed overnight under an argon atmosphere, then concentrated *in vacuo*. The residue was suspended in a few drops of water and the resulting mixture was treated with a few pieces of dry ice to reduce its basicity. The mixture was filtered, and the precipitate was washed with ether and dried under reduced pressure. The solid obtained was refluxed in HCO_2Et (10 ml) for 9 h under an argon atmosphere. After removal of HCO_2Et *in vacuo*, the residue was washed with $CHCl_3$. The washings were filtered, and the filtrate was concentrated *in vacuo* to afford the *N*-formate (**7**) (390 mg, 87%) as a white powder. IR ν_{max}^{Nujol} cm^{-1}: 3150—3450, 1645.

(2*R*,3*R*)-2-Formylamino-3-(4-hydroxyphenyl)-1,3-propanediol (8) A mixture of the *N*-formate (**7**) (423 mg, 1.41 mmol), 10% palladium on carbon (330 mg), and ethanol (20 ml) was stirred under H_2 for 1 h. The catalyst was filtered off, and the filtrate was evaporated *in vacuo* to afford the phenol (**8**) as crystals in quantitative yield, $[\alpha]_D$ −34.20° (c=0.80, MeOH), mp, 137—139 °C. IR ν_{max}^{film} cm^{-1}: 3200—3400, 1655. MS m/z: 211 (M^+). ^{1}H-NMR (90 MHz in CD_3OD) δ: 3.52 (1H, d, J=9.2 Hz), 3.58 (1H, d, J=9.2 Hz), 3.78 (1H, s), 4.00 (1H, s), 4.09 (1H, m), 4.66 (1H, d, J=4.0 Hz), 4.80 (1H, s), 6.73 (2H, d, J=8.1 Hz), 7.20 (2H, d, J=8.1 Hz), 7.72 (1H, s), 8.02 (1H, s). *Anal.* Calcd for $C_{10}H_{13}NO_4$: C, 56.86; H, 6.20; N, 6.63. Found: C, 56.53; H, 6.17; N, 6.65.

(4*R*,5*R*)-2,2-Dimethyl-4-(4-hydroxyphenyl)-5-formylamino-1,3-dioxolane (9) A solution of the phenol (**8**) (208 mg, 0.99 mmol), 2,2-dimethoxypropane (4 ml), and *dl*-camphorsulfonic acid (12 mg, 0.05 mmol) in acetone (4 ml) was stirred at room temperature for 3 h. Then 2% aqueous Na_2CO_3 (40 ml) was added to the reaction mixture, and the whole was concentrated *in vacuo* to give a residue, which was extracted with $CHCl_3$. The $CHCl_3$ extract was washed with brine, dried over K_2CO_3, and evaporated. The residue was purified by flash chromatography (ethyl acetate–hexane (12:5)) to afford the acetonide (**9**) (165 mg, 67%) as a colorless glass, $[\alpha]_D$ +6.62° (c=1.56, MeOH). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3250, 1675. MS m/z: 251 (M^+). ^{1}H-NMR (90 MHz in $CDCl_3$) δ: 1.54 (3H, s), 1.58 (3H, s), 3.83 (1H, dd, J=2.0, 12.3 Hz), 4.24 (2H, m), 5.14 (1H, br s), 6.47 (1H, d, J=8.1 Hz), 6.69 (2H, d, J=8.7 Hz), 7.14 (2H, d, J=8.7 Hz), 7.52 (1H, s), 7.69 (1H, s).

(4*R*,5*R*)-2,2-Dimethyl-4-[4-(2-bromoethyloxyphenyl)]-5-formylamino-1,3-dioxolane (10) A mixture of the acetonide (**9**) (50 mg, 0.20 mmol), 1,2-dibromoethane (172 μl, 2.0 mmol), potassium carbonate (138 mg, 1.0 mmol), and ethanol (3 ml) was stirred at 90 °C under argon for 40 h. The reaction mixture was diluted with ethyl acetate. The solution was washed with water, dried over $MgSO_4$ and evaporated *in vacuo* to afford an oil, which was purified by flash chromatography. Elution with ethyl acetate–hexane (4:1) gave the bromide (**10**) (54 mg, 75%) as a colorless oil, $[\alpha]_D$ +5.45° (c=0.88, MeOH). IR ν_{max}^{film} cm^{-1}: 3430, 1680. MS m/z: 357 (M^+). ^{1}H-NMR (90 MHz in $CDCl_3$) δ: 1.54 (3H, s), 1.58 (3H, s), 3.61 (2H, t, J=6.2 Hz), 3.85 (1H, dd, J=2.3, 12.5 Hz), 4.20 (2H, m), 4.25 (2H, t, J=6.2 Hz), 5.15 (1H, br s), 6.25 (1H, d, J=9.0 Hz), 6.86 (2H, d, J=9.0 Hz), 7.24 (2H, d, J=9.0 Hz), 7.97 (1H, s).

***O*,*O*-Isopropylidene-(−)-bursatellin (11)** A solution of the bromide (**10**) (54 mg, 0.15 mmol) in DMSO (2 ml) was treated with NaCN (11 mg, 0.22 mmol) and NaH_2PO_4 (5.4 mg, 0.05 mmol), and the whole was stirred overnight under an argon atmosphere. The reaction mixture was diluted with ethyl acetate, and the solution was washed three times with aqueous NaCl, dried over $MgSO_4$, and evaporated *in vacuo*. The residue was purified by preparative TLC (ethyl acetate–hexane (10:1)) to give the cyanide (**11**) (33 mg, 73%) as a colorless oil, $[\alpha]_D$ +1.49° (c=0.97, $CHCl_3$). IR ν_{max}^{film} cm^{-1}: 3430, 2260, 1680. MS m/z: 304 (M^+). ^{1}H-NMR (90 MHz in $CDCl_3$) δ: 1.55 (3H, s), 1.58 (3H, s), 2.81 (2H, t, J=6.4 Hz), 3.86 (1H, dd, J=2.2, 12.5 Hz), 4.17 (2H, t, J=6.4 Hz), 4.28 (2H, m), 5.16 (1H, br s), 6.17 (1H, d, J=9.0 Hz), 6.86 (2H, d, J=8.9 Hz), 7.26 (2H, d, J=8.9 Hz), 7.99 (1H, s).

(−)-Bursatellin (1) A solution of the foregoing cyanide (**11**) (32 mg, 0.11 mmol) in 80% aqueous acetic acid (4 ml) was stirred at 100 °C for 30 min. After the solvent had been removed *in vacuo*, the residue was purified by preparative TLC ($CHCl_3$–MeOH (10:1)) to afford (−)-bursatellin (**1**) (20 mg, 72%) as a colorless glass, $[\alpha]_D$ −8.0° (c=0.29, MeOH). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3200—3400, 2250, 1660. ^{1}H-NMR (90 MHz in CD_3OD) δ: 2.90 (2H, t, J=5.9 Hz), 3.52 (1H, m), 3.63 (1H, dd, J=5.8, 10.8 Hz), 4.10 (1H, m), 4.17 (2H, t, J=5.9 Hz), 4.95 (1H, d, J=4.2 Hz), 6.91 (2H, d, J=8.7 Hz), 7.33 (2H, d, J=8.7 Hz), 8.00 (1H, s).

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