Russian Journal of Organic Chemistry, Vol. 38, No. 6, 2002, pp. 855–857. Translated from Zhurnal Organicheskoi Khimii, Vol. 38, No. 6, 2002, pp. 898–900.

Alternative Procedure for the Synthesis of (+)-Tavacpallescencine Precursor

A. K. Banerjee, V. Vera, and S. Laya

Chemical Center, IVIC, p/o box 21827 Caracas 1020-A, Venezuela

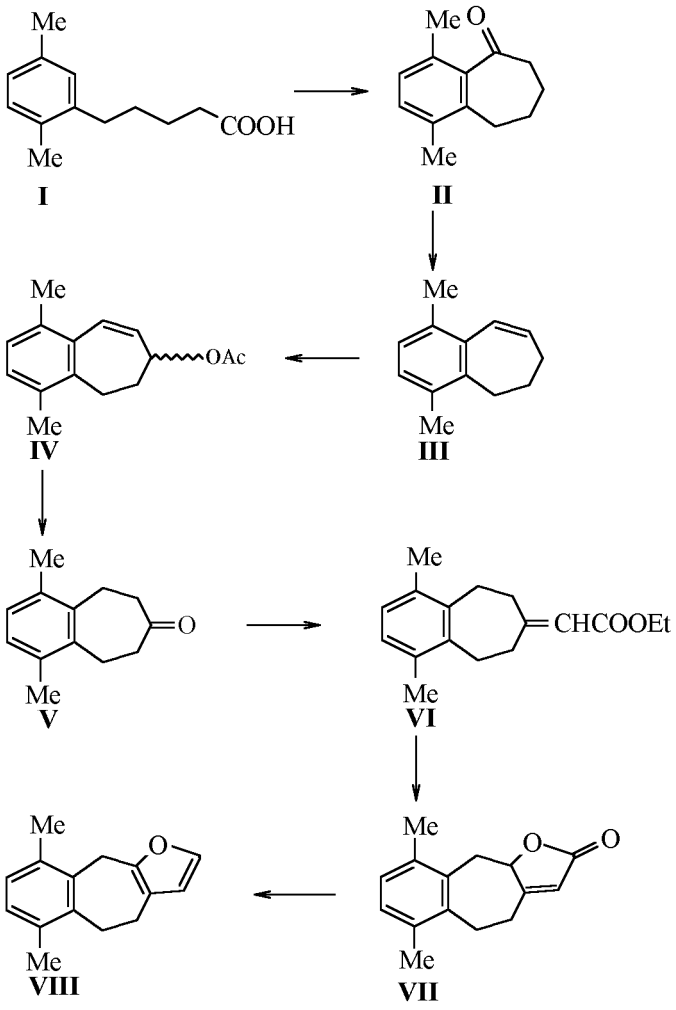
Received December 14, 2001

Abstract–A conversion of dimethylbenzo[d]suberone prepared from 5-chlorovaleric acid into butenolide, a precursor of tavacpallescencine, was described.

Recently Ho and Linn [1] reported on the synthesis of butenolide (**VII**) and its conversion into a sesquiterpene tavacpallescencine (**VIII**) by reduction with diisobutylaluminum hydride. In this study a complete synthesis of tavacpallescencine (**VIII**) was performed for the first time. In connection with our research on terpenoids we attempted to develop an alternative synthesis of butenolide (**VII**) as a precursor in the course of complete synthesis of compound **VIII**. Here we report on details of this study.

Friedel–Krafts alkylation of *p*-xylene with 5-chlorovaleric acid in the presence of aluminum chloride furnished acid **I** in 94% yield. The latter was subjected to cyclization by treating with polyphosphoric acid to obtain ketone **II** in 80% yield. The ketone was converted into olefin **III** in 73% yield by heating with 2,4-pentanediol and *p*-tolyenesulfonic acid in toluene [2]. The treating of olefin **III** with manganese(III) acetate dihydrate [3] and catalytic quantity of potassium bromide in acetic acid provided a mixture of acetate **IV** stereoisomers in 50% yield (according to ^{1}H NMR data). After alkaline hydrolysis followed by hydrogenation and oxidation with Jones' reagent [4] dimethylbenzosuberone (**V**) was obtained with spectral characteristics identical to those published [1]. Thus the sequence of transformation performed provides an alternative route for the preparation of benzosuberone (**V**).

Allyl oxidation of olefin **III** with Collins' reagent [5] or with a mixture CrO_3-3,5-dimethylpyrazole did not provide the α,β-unsaturated ketone in sufficient yield. Therefore our preliminary plan to hydrogenate the α,β-unsaturated ketone to obtain benzosuberone (**V**) was impossible. The benzosuberone (**V**) was subjected to Wittig reaction (instead of Emmons–Wodsfort condensation) by heating with ethoxycarbonylmethylenetriphenylphosphorane (Ph_3P=CHCOOEt) in the presence of catalytic quantity of benzoic acid [6] in toluene. Ester **VI** of the α,β-unsaturated acid was obtained in 90% yield. In the absence of benzoic acid the yield of ester attained 53%.. The conversion of dimethylbenzosuberone (**V**) into ester **VI** did not occur sufficiently well in the presence of cinnamic acid.



1070-4280/01/3806-855$27.00 © 2002 MAIK "Nauka/Interperiodica"

We tested several procedures for oxidative cyclization of ester **VI**. The desired result was obtained by heating ester **VI** with selenium(IV) oxide and acetic acid [1]. Butenolide (**VII**) was obtained in 70% yield as a solid with spectral characteristics consistent with the published data [1].; however in [1] was not published whether compound **VII** was solid or liquid. Since butenolide (**VII**) was transformed into tavacpallescencine (**VIII**) our alternative procedure for preparation of butenolide (**VII**) is a part of the complete synthesis of (+)-tavacpallescencine (**VIII**).

It may be stated in conclusion that we have developed an alternative route for the synthesis of butenolide (**VII**). Also a simple preparation method was found for dimethylbenzosuberone (**V**), and it was shown that Wittig reaction was as suitable to the synthesis of conjugated ester **VI** as Emmons–Wodsfort condensation. The yields of the most compounds described in this report are fairly well.

EXPERIMENTAL

IR spectra were recorded on spectrometer Nicolet FT, and ^{1}H NMR spectra were registered on spectrometer Bruker (300 MHz) from solutions in $CDCl_3$. Mass spectra were measured on Kratus MS 25RFA instrument, and chromatograms were obtained on gas chromatograph Hewlett-Packard 5890 Quadrupolar 5972, series S. To column chromatography was applied silica gel Merck 60, 70–230 mesh, 60 Å, TLC plates were covered with silica gel $60F_{254}$. layer thickness 0.02 mm, spots visualized under UV light. Microanalyses were carried out in the Chemical Department of IVIC.

3′,6′-Dimethyl-1,2-benzocyclohepten-3-one (II). To a suspension of 7.79 g of freshly sublimed aluminum chloride in 20 ml of anhydrous xylene cooled to 15°C was added 4.01 g of 5-chlorovaleric acid. The mixture was stirred for 2 h at 15°C and then heated to 89°C for 1 h. To the reaction mixture cooled to 15°C was added dropwise 10 ml of concn. HCl and water. Reaction products were extracted into chloroform, the extract was several times treated with 10% water solution of sodium hydroxide, the alkaline water solution was acidified by concn. HCl, and acid **I** was extracted into chloroform. The solution was diluted with water, the products were extracted with ether, the extract was washed with NaCl solution, dried with $MgSO_4$, and evaporated in a vacuum. We obtained 5.65 g (94%) of acid **I**, thick yellow substance. Mass spectrum, *m/z* 206 $[M]^+$, 119 $[M–CH_2COOH]^+$. IR spectrum, cm^{-1}: 3000–2000 (COOH), 1712 (CO). Acid I was subjected to cyclization without further purification.

To polyphosphoric acid (13.5 g) heated to 70°C was added 4.04 g of acid **I**, and the mixture was stirred for 2 h at the same temperature. Then the reaction products were extracted with ether, the extract was washed with 10% water solution of sodium hydrogen carbonate and with water. After the common workup we isolated oily substance that was subjected to vacuum distillation to afford 2.94 g (80%) of ketone **II**, bp 125–128°C (1 mm Hg). Mass spectrum, *m/z* 188 $[M]^+$. ^{1}H NMR spectrum, δ, ppm: 6.89 s (2H, aromatic protons), 2.58–2.61 m (2H, H^7) and 2.31 s (6H, 2 CH_3–Ph). Found, %: C 82.33; H 8.77. $C_{13}H_{16}O$. Calculated, %: C 82.93; H 8.57.

3′,6′-Dimethyl-1,2-benzo-1,3-cycloheptadiene (III). A solution of ketone **II** (1.52 g), 2,4-pentanediol (3.33 g), and *p*-toluenesulfonic acid (45 mg) in 75 ml of anhydrous toluene was boiled in a device equipped with a Dean-Stark trap for 48 h. The dark-yellow solution obtained was washed with 5% water solution of sodium hydrogen carbonate. After the common workup an oily product was obtained that was subjected to chromatography (eluent hexane). Olefin **III** was separated in amount 1.03 g (73%). Mass spectrum, *m/z*: 172 $[M]^+$. IR spectrum, cm^{-1}: 1605 (C=C). ^{1}H NMR spectrum, δ, ppm: 7.14–6.91 m (2H, aromatic protons), 6.67–6.42 m (1H, vinyl proton), 2.92–2.83 m (2H, H^7), 2.50–2.35 m (5H, CH_3–Ph and CH_2–C=C), 2.32 s (3H, CH_3–Ph). Found, %: C 91.08; H 9.58. $C_{13}H_{16}$. Calculated, %: 90.64; H 9.36.

3′,6′-Dimethyl-1,2-benzo-1,3-cycloheptadien-5-yl acetate (IV). To a solution of 1.18 g of manganese(III) acetate dihydrate in 15 ml of acetic acid heated to 70°C was added 1.01 g of olefin **III** and 55 mg of potassium bromide. The mixture obtained was heated to 70°C for 6 h, and the reaction products were extracted into chloroform. After the common workup we obtained brown oily substance that was subjected to chromatography (eluent hexane–ethyl ether, 8:2) to isolate 682 mg of oily acetate **IV** (50%). Mass spectrum, *m/z*: 230 $[M]^+$. IR spectrum, cm^{-1}: 1735 (CO). ^{1}H NMR spectrum, δ, ppm: 6.99 d (2H, aromatic protons, *J* 9 Hz), 6.73–6.69 d.d (1H, vinyl proton, $J_{3,4}$ 12; $J_{3,5}$ 1.7 Hz), 5.95–5.91 d.d (1H, vinyl proton, $J_{4,3}$ 12; $J_{4,5}$ 4 Hz), 5.82–5.78 d.t (1H, HCOAc, $J_{5,4}$ 4 Hz, $J_{5,6ax}$??), 2.63–2.88 m (4H), 2.34 s (3H, Me–Ph), 2.32 s (3H, Me–Ph), 2.12 s (3H, OAc). Found, %: C 78.63; H 8.08. $C_{15}H_{18}O_2$. Calculated, %: C 78.23; H 7.88.

3′,6′-Dimethyl-1,2-benzo-1,3-cyclohepten-5-one (benzosuberone) (V). To a 5% solution of sodium hydroxide in methanol (18 ml) was added 305 g of acetate (**IV**), and the mixture was stirred for 24 h at room temperature. After the common workup we obtained an unsaturated alcohol (230 mg). IR spectrum: 3384 cm^{-1} (OH). The solution of the alcohol (230 mg) in ethanol (12 ml) was subjected to hydrogenation on PtO_2 (59 mg). A saturated alcohol was obtained (202 mg, 90%). Mass spectrum, *m/z*: 190 $[M]^+$, 172 $[M–H_2O]^+$. IR spectrum: 3360 cm^{-1} (OH).

To the solution of the saturated alcohol obtained (202 mg) in 20 ml of acetone cooled to 0°C was added 1 ml of Jones' reagent, and the mixture was stirred for 14 h at 0°C. After the standard workup followed by chromatographic purification (eluent hexane–ethyl ether, 4:6) benzosuberone (**V**) was obtained (224 mg, 90%). Mass spectrum, *m/z*: 188 $[M]^+$. IR spectrum: 1701 cm^{-1} (CO). ^{1}H NMR spectrum, δ, ppm: 7.06 s (1H) and 7.01 s (1H, aromatic protons), 2.85–2.89 s (4H), 2.55–2.61 m (4H), 2.35 s (6H, $2CH_3$–Ph). Found, %: C 83.33; H 8.77. $C_{13}H_{16}O$. Calculated, %: C 82.93; H 8.57.

Ethyl 2-(3′,6′-dimethyl-1,2-benzocyclohepten-5-ylidene)acetate (VI). To a solution of 185 mg of ketone (**V**) in 10 ml of toluene was added ethoxycarbonylmethylenetriphenylphosphorane and benzoic acid (30 mg), and the mixture was boiled under argon atmosphere for 24 h. On evaporation of the solvent and chromatographic purification (eluent hexane–ethyl ether, 7:3) we obtained ester **VI** (234 mg, 90%). Mass spectrum, *m/z*: 258 $[M]^+$, 184 $[M–HCOOEt]^+$. IR spectrum: 1712 cm^{-1} (CO). ^{1}H NMR spectrum, δ, ppm: 6.99 s (2H, aromatic protons), 5.72 s (1H, vinyl proton), 4.16–4.23 q (2H, $OC\underline{H}_2CH_3$), 2.33 s (6H, 1,4-Me), 1.32 m (3H, $\underline{Me}CH_2O$, *J* 7 Hz). Found, %: C 79.437; H 8.78. $C_{17}H_{22}O_2$. Calculated, %: C 79.03; H 8.58.

6,9-Dimethyl-4,5,10,10a-tetrahydro-2*H*-benzo-[5,6]cyclohepta[1,2-b]furan-2-one (VII). To a solution of 202 mg of ether **VI** in 10 ml of glacial acetic acid was added 99 mg of selenium(IV) oxide, and the mixture was boiled for 6 h. After the standard workup we obtained yellow oily compound that was subjected to chromatography (eluent hexane–ethyl acetate, 3:7) to isolate 131 mg (70%) of butenolide (**VII**), mp 138–141°C (from ether). Mass spectrum, *m/z*: 228 $[M]^+$. IR spectrum: 1760 cm^{-1} (CO). ^{1}H NMR spectrum, δ, ppm: 6.98 br.s (2H, aromatic protons), 5.76 s (1H, vinyl proton), 4.66–4.77 m (1H), 3.29–3.35 d.d (1H, *J* 3.6, 14 Hz), 3.06–3.18 m (2H), 2.70–2.91 m (3H), 2.79–2.83 m (1H), 2.55–2.64 m (1H), 2.36 s (3H), 2.31 s (3H, 6,9-Me). Found, %: C 79.32; H 7.26. $C_{15}H_{16}O_2$. Calculated, %: C 78.92; H 7.06.

REFERENCES

1. Ho, T.L., Linn, Y.J, *J. Chem. Soc., Perkin Trans. I*, 1999, p. 1207.
2. Vuligonda, V., Lin, Y., and Chandraratna, R.A.S, *Tetrahedron Lett.*, 1966, vol. 37, p. 1941.
3. Gilmore, J.R. and Mellor, S.M, *J. Chem. Soc.*, 1971, p. 2355.
4. Bowers, A., Halsall, T.G., Jones, E.R.H., and Li-min, A.J, *J. Chem. Soc*.. 1953, p. 2548.
5. Collins, J.C., Hess, W.W., and Frank, F.J, *Tetrahedron Lett.*, 1968, p. 3363.
6. Ruechardt, C., Eichter, S., and Panse, P, *Angew. Chem., Int. Ed.*, 1963, vol. 2., p. 619.