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A Modified Synthesis of (±)-Occidentalol

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Summary. An alternative synthesis of methyl 4α,8aβ-dimethyl-3-oxo-*trans*-perhydronaphthalene-6β-carboxylate is described.

Keywords. Occidentalol; Bromination; Dehydrobromination; Cyclic ether; Esterification.

Eine modifizierte Synthese von (±)-Occidentalol

Zusammenfassung. Es wird eine alternative Synthese von Methyl-4α,8aβ-dimethyl-3-oxo-*trans*-perhydronaphthalin-6β-carboxylat beschrieben.

Introduction

In connection with several terpene syntheses, the synthesis of the racemic ketoester **13** has been reported [1]. Its spectroscopic properties have been found to be identical with those reported for the optically active ketoester **13** [2]. It proved to be a potential intermediate for the synthesis of the eudesmane-type sesquiterpene occidentalol (**14**). For **14**, several syntheses have been reported [3]. An alternative approach for the synthesis of the ketoester **13** that cannot only be utilized for the synthesis of racemic occidentalol **14** but can also play an important role in the synthesis of other sesquiterpenoid compounds is presented.

Results and Discussion

Bromination of **1** with pyridinium bromide perbromide [4] followed by dehydrobromination using lithium carbonate and lithium bromide in dimethylformamide yielded the α,β-unsaturated ketone **2** in 50% yield. Addition of lithium dimethylcopper to ketone **2** afforded the adduct **3**. On the basis of Refs. [5–7], the newly introduced methyl group was assigned to be α-configurated. Upon bromination and subsequent dehydrobromination by the procedure already described, **3** was converted to the α,β-unsaturated ketone **4** which on hydrogenation with Pd-C (5%) produced the saturated ketone **5** in excellent yield. The assignment of the β-configuration of 6-Me followed by analogy [8]. Reduction of the carbonyl group of the ketone **5** with $LiAlH_4$ formed the alcohol **6** in 60% yield. It exhibited a ^1H NMR signal centered at $\delta = 3.92$ ppm indicating an α-oriented hydroxyl group [9].

Irradiation of **6** together with lead tetraacetate and iodine with a tungsten lamp afforded the cyclic ether **7**. Its spectroscopic data (NMR and MS) corroborated the assumed structure. Oxidation of **7** with chromic acid in acetic acid at room temperature afforded the ketoacid **8**. It was esterificated with methanol in presence of boron trifluoride diethyl ether to yield the ketoester **9** (42%). Reduction of **9** with sodium borohydride in methanol produced an alcohol. Its tosyl derivative formed the olefin **10** upon heating with lithium bromide and lithium carbonate in dimethylformamide. The latter proved to be susceptible to aerial oxidation. It was converted to the known ester **11** [1] by hydrogenation with *Adams'* catalyst in acetic acid. Its spectroscopic data were identical with those reported and its identity was also confirmed by TLC comparison with an authentic specimen [1].

The ester **11** was converted to the ketoester **13** by treatment with boron tribromide, sodium iodide, and 15-crown-5 in CH_2Cl_2 [10]. The resulting alcohol **12** was oxidized without purification with pyridinium chlorochromate in dichloromethane [11] to obtain the ketoester **13** in satisfactory yield. The identity of **13** was confirmed by comparing its spectroscopic data and TLC with an authentic specimen [1].

In the previous synthesis of the ketoester **13** [1], the introduction of the 6-COOMe group has been achieved from the 6-CO group *via* reduction, tosylation, cyanation, hydrolysis, and esterification. The process involves many steps and, moreover, uses the poisonous reagent NaCN. This inconvenience has been overcome in the present synthesis. In our alternative approach, the process of demethoxylation involves one step less than in the previously reported synthesis [1]. In addition, the yields of ester **11** and ketoester **13** have been slightly improved. Therefore, the present method appears to be more attractive for the synthesis of occidentalol.

Experimental

Unless stated otherwise, IR spectra were measured on a Nicolet FT instrument. ^1H NMR spectra were recorded on Varian A-90 spectrometer at 90 MHz in $CDCl_3$ using *TMS* as internal standard. Mass spectra were scanned on a Dupont 21-492B apparatus. The expression "workup" indicates that the solution is diluted with water, extracted with ether, washed with brine, dried ($MgSO_4$), and evaporated under reduced pressure. Column chromatography was carried out on silica 60 (Merck). Microanalyses were carried out in the Department of Chemistry, IVIC, Caracas; experimental and calculated values (C, H) agreed satisfactorily.

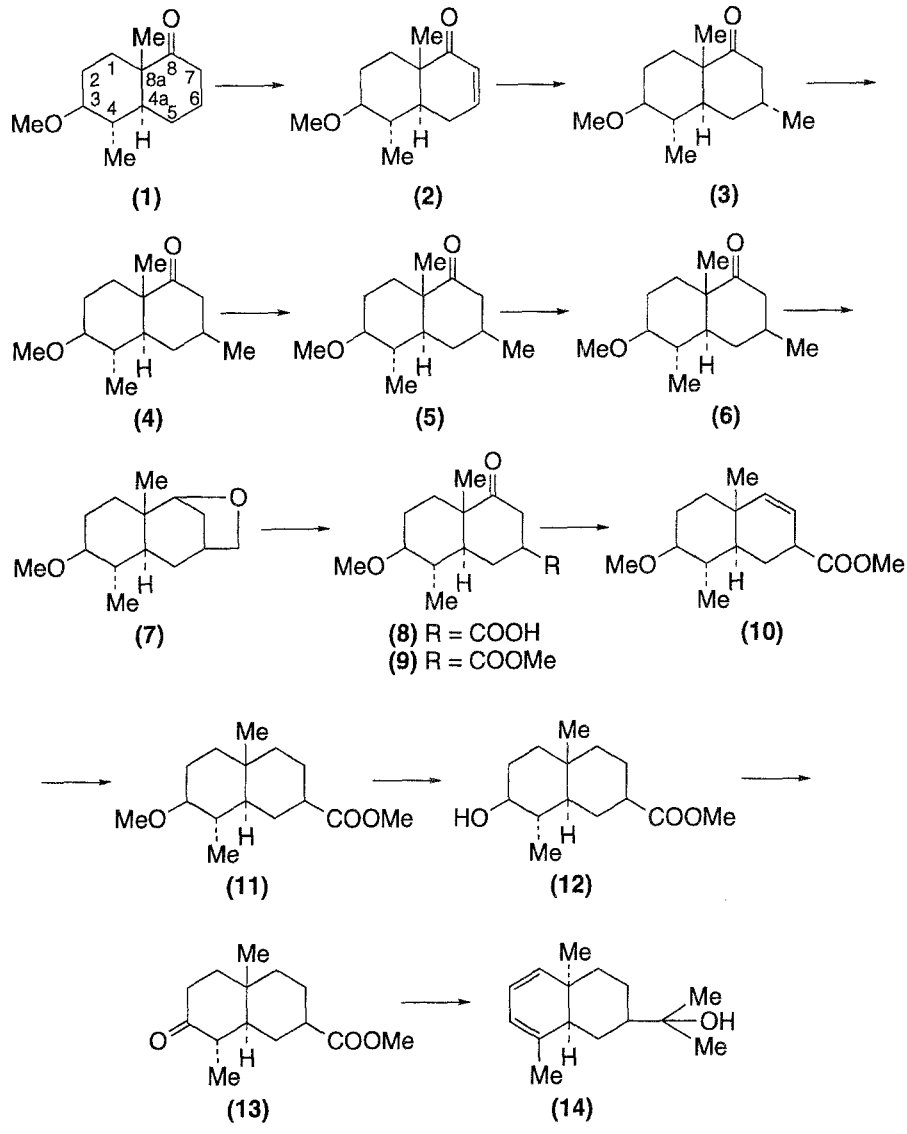
3-Methoxy-4α-8a-dimethyl-1,2,3,4,4a,5-hexahydro-naphthalene-8-one (**2**; $C_{13}H_{20}O_2$)

A mixture of 900 mg **1**, 1.45 g pyridinium bromide perbromide in 20 ml ethanol, and 40 ml $CHCl_3$ was stirred at room temperature for 50 min. Workup afforded 1.12 g of an oily material which was heated in 25 ml *DMF* at 130–160 °C for 4 h with 600 mg lithium carbonate and 600 mg lithium bromide. Workup and purification (hexane: ether = 8:2) afforded **2** (445 mg, 50%).

IR: $\nu_{max} = 1645\,cm^{-1}$ (CO); ^1H NMR: $\delta = 1.03$ (d, 3H, $J = 6$ Hz, 4-Me), 1.12 (s, 3H, 8a-Me), 3.52 (s, 3H, OMe), 5.75 (1H), 5.85 (1H, vinyl protons) ppm; MS: $m/z = 208$ (M^+).

3-Methoxy-4α,6,8a-trimethyl-trans-perhydronaphthalene-8-one (**3**; $C_{14}H_{24}O_2$)

To 1.46 g anhydrous copper iodide in 15 ml anhydrous ether, 1 ml methyllithium (1.6 *M*) was added at 0 °C. After 15 min, 400 mg **2** in 10 ml ether were added dropwise and the mixture was stirred at 0 °C



for 2 h. Workup followed by chromatographic purification (hexane: ether = 6:4) yielded **3** (177 mg, 41%).

IR: $\nu_{max} = 1710\,cm^{-1}$ (CO); ^1H NMR: $\delta = 1.02$–1.04 (6H, 4-Me and 6-Me), 1.12 (s, 3H, 8a-Me), 3.55 (s, 3H, OMe) ppm; MS: $m/z = 224$ (M^+).

3-Methoxy-4α-6,8a-trimethyl-1,2,3,4,4a,5-hexahydronaphthalene-8-one (**4**; $C_{14}H_{22}O_2$)

170 mg of the ketone **3** and 235 mg pyridinium bromide perbromide dissolved in 15 ml ethanol and 30 ml chloroform were stirred at room temperature for 45 min. Workup yielded an oil (185 mg) which was heated at 130–160° in 15 ml *DMF* for 4 h with lithium carbonate (150 mg) and lithium bromide (150 mg). After chromatography (hexane: ether = 4:6), the ketone **4** (67 mg, 40%) was obtained.

IR: $\nu_{max} = 1660\,cm^{-1}$ (CO); ^1H NMR: $\delta = 1.04$ (d, 3H, $J = 6$ Hz, 4-Me), 1.12 (s, 3H, 8a-Me), 1.62 (s, 3H, 6-Me), 5.82 (1H, 7-H) ppm; MS: $m/z = 222$ (M^+).

3-Methoxy-4α,6β,8a-trimethyl-perhydronaphthalene-8-one (**5**; $C_{14}H_{24}O_2$)

80 mg of ketone **4** was hydrogenated with 200 mg Pd-C (5%) in 30 ml absolute methanol. Chromatography (hexane: ether = 6:4) afforded the oily saturated ketone **5** (70 mg, 86%).

IR: $\nu_{max} = 1708\,cm^{-1}$ (CO); ^1H NMR: $\delta = 1.04$–1.08 (6H, 4-Me and 6-Me), 1.12 (s. 3H, 8a-Me), 3.52 (s, 3H, OMe) ppm; MS: $m/z = 224$ (M^+).

3-Methoxy-4α,6β,8a-trimethyl-perhydronaphthalene-8β-ol (**6**; $C_{14}H_{26}O_2$)

To 300 mg of **5** dissolved in 50 ml dry tetrahydrofuran, $LiAlH_4$ (80 mg) was added and the mixture was refluxed for 4 h. Workup and chromatography (hexane: ether = 3:9) gave **6** (181 mg, 60%).

IR: $\nu_{max} = 3280\,cm^{-1}$ (OH); ^1H NMR: $\delta = 1.02$–1.07 (6H, 4a-Me and 6-Me), 1.12 (s, 3H, 8a-Me), 3.92 (m, $\nu_{1/2} = 8$ Hz, 8-H), 3.56 (s, 3H, OMe) ppm; MS: $m/z = 208$ (M^+-H_2O).

Lead tetraacetate oxidation of **6**

A mixture of 1 g lead tetraacetate and 1 g anhydrous calcium carbonate was heated in 30 ml cyclohexane for 30 min. To the suspension a solution of 180 mg of **6** in 5 ml cyclohexane was added, followed immediately by 350 mg iodine. The resulting mixture was irradiated for 1.5 h with two Phillips 250 W photo lamps. Workup and chromatography (hexane) yielded **7** (53 mg, 30%).

^1H NMR: $\delta = 1.04$ (d, 3H, $J = 6$ Hz, 4-Me), 1.12 (s, 3H, 8a-Me), 3.34 (m, 2H, OCH_2), 3.42 (s, 3H, OMe) ppm; MS: $m/z = 224$ (M^+).

Methyl-4α-8a-dimethyl-8-keto-trans-perhydronaphthalene-6β-carboxylate (**9**; $C_{15}H_{24}O_4$)

To 500 mg **7** dissolved in 10 ml acetic acid (99%), a solution of 100 mg chromic acid in 10 ml acetic acid was added. Stir for 40 h at room temperature and workup yielded the acid **8** (300 mg), a semi-solid material.

IR: $\nu_{max} = 1701$ (unresolved acid and ketonic C=O); MS: $m/z = 209$ (M^+-COOH).

The acid **8** was dissolved in 200 ml freshly distilled boron trifluoride-diethyl ether (200 mg) without further purification, treated with 1 ml of dry methanol, and heated under reflux for 24 h. Workup and chromatography (hexane: ether = 1:1) afforded the ester **9** (252 mg, 42%).

IR: $\nu_{max} = 1705\,cm^{-1}$ (ketonic CO); ^1H NMR: $\delta = 1.05$ (d, 3H, $J = 6$ Hz, 4a-Me), 1.12 (s, 3H, 8a-Me), 3.42 (s, 3H, OMe), 3.58 (s, 3H, OMe) ppm; MS: $m/z = 268$ (M^+).

Methyl-3-methoxy-4α,8aβ-dimethyl-trans-perhydronaphthalene-6β-carboxylate (**11**; $C_{15}H_{26}O_3$)

To 250 mg of **9** dissolved in 25 ml methanol and cooled to 0 °C, 60 mg of sodium borohydride, (Merck) were added. Workup yielded 260 mg of an alcohol. (IR: $\nu_{max} = 3580\,cm^{-1}$, OH). Its tosylate (280 mg), prepared by the standard procedure, was heated in 15 ml *DMF* for 2 h with 100 mg lithium carbonate and 100 mg lithium bromide. Workup and chromatography (hexane: ether = 2:8) produced the olefin **10** (180 mg).

IR: $\nu_{max} = 1720\,cm^{-1}$ (CO); ^1H NMR: $\delta = 1.03$ (d, 3H, $J = 6$ Hz, 4-Me), 1.12 (s, 3H, 8a-Me), 3.42 (s, 3H, OMe), 3.56 (s, 3H, OMe), 5.62–5.68 (m, 2H, vinyl protons) ppm.

10 (180 mg) was hydrogenated in acetic acid (5 ml) with PtO_2 (60 mg) at atmospheric pressure for 1 h. The usual workup yielded ester **11** (165 mg, 70%) [1].

IR: $\nu_{max} = 1718\,cm^{-1}$ (CO); ^1H NMR: $\delta = 0.88$ (d, 3H, $J = 6$ Hz, 4-Me), 1.05 (s, 3H, 8a-Me), 3.45 (s, 3H, OMe), 3.54 (s, 3H, OMe) ppm; MS: $m/z = 254$ (M^+).

Methyl-4a,8aβ-dimethyl-3-oxo-trans-perhydronaphthalene-6β-carboxylate (**13**; $C_{14}H_{22}O_3$)

To a solution of 165 mg **11** in 2 ml of dry CH_2Cl_2, 25 ml of a 0.3 *M* solution of 15-crown-5 in CH_2Cl_3 saturated with sodium iodide were added, followed by the addition of 3 ml boron tribromide (1 *M* in

CH_2Cl_2) under argon at −10 °C. The mixture was then stirred for 3 h at the same temperature. The usual workup followed by filtering the resulting product over a column of silica gel (eluant: ether: hexane = 8:2) afforded **12** (110 mg); IR: $\nu_{max} = 3320\,cm^{-1}$ (OH).

To a solution of 110 mg **12** in dry CH_2Cl_2 (10 ml) at 0–5 °C, pyridinium chlorochromate (120 mg) was added, and the mixture was stirred at room temperature for 2 h. Workup and chromatography (hexane: ether = 7:3) afforded the oily keto ester **13** (90 mg, 58%).

IR: $\nu_{max} = 1718\,cm^{-1}$ (CO); ^1H NMR: $\delta = 0.94$ (d, 3H, $J = 6$ Hz, 4-Me), 1.03 (s, 3H, 8a-Me), 3.65 (s, 3H, OMe) ppm; MS: $m/z = 238$ (M^+).

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References

[1] Banerjee AK, Canudas N, Cabrera-Nieto G, Peña-Matheud CA (1990) J Chem Res (S) 266
[2] Hortmann AG, Martinelli JE, Wang Y (1969) J Org Chem **34**: 732
[3] Heathcock CH, Graham SL, Pirrung MC, Plavac F, White CT (1983) Total synthesis of sesquiterpenes. In: Apsimon J (ed) Total synthesis of natural products, vol 5. Wiley, New York, pp 143
[4] Purchased from Aldrich Chemical Company
[5] Heathcock CH (1973) Total synthesis of sesquiterpenes. In: Apsimon J (ed) Total synthesis of natural products, vol 2. Wiley, New York, pp 309
[6] Marshall JA, Greene AE (1971) J Org Chem **36**: 2035
[7] Marshall JA, Brady SF (1970) J Org Chem **35**: 4068
[8] Coates RM, Shaw JE (1968) Chem Communs: 47
[9] Banerjee AK, Hurtado H, Laya M, Acevedo JC, Alvárez J (1985) J Chem Soc Perkin Trans I, 267
[10] Banerjee AK, Laya-Mimo M (1995) Syn Communs **25**: 1035
[11] Corey EJ, Suggs JW (1975) Tetrahedron Lett: 2647

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