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A HIGHLY STEREOSELECTIVE TOTAL SYNTHESIS OF (±)-ISOALANTOLACTONE

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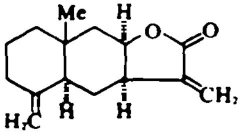
Abstract—(±)-Isoalantolactone (1) has been synthesized by a highly stereoselective route from the versatile bicyclic ketone, *trans*-5-methylene-9-methyl-2-decalone 2. Three major points in the synthesis involve (a) introduction of the acetic acid side chain; (b) stereoselective reduction of the ketone function yielding *cis*-lactone 6; and (c) introduction of the α-methylene group onto the butyrolactone ring.

Isoalantolactone[1] 1 is a member of the eudesmane class of sesquiterpenes and contains, as one of its structural features, the α-methylene-γ-butyrolactone moiety which has attracted much synthetic interest recently[2] because of its presence in compounds demonstrating considerable biological activity as allergenic agents,[3] growth inhibitors,[4] antibacterial agents,[5] and antitumor agents.[6]

As part of our interest in synthetic approaches to both eudesmane sesquiterpenes[7] and α-methylene-γ-butrolactones[2i] we undertook an investigation of the synthesis of (±)-isoalantolactone. We now wish to report a highly stereoselective total synthesis of this compound.



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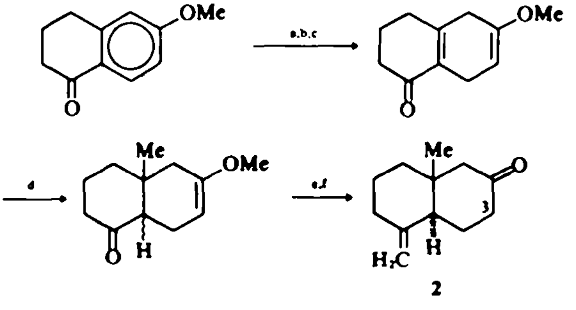
Earlier in a study of general synthetic approaches to the eudesmane sesquiterpenoids we described a convenient synthesis of *trans*-5-methylene-9-methyl-2-decalone 2[7] (Scheme I) which served as our starting material in this synthesis. This compound was also the starting material used by Minato and Horibe[2f] in their synthesis of (±)-isoalantolactone.

Our attention was concentrated on three major points in the elaboration of compound 2 to (±)-isoalantolactone. The first was the problem of introduction of an acetic acid side chain at C-3. Other workers[2f,8] have employed enamine alkylation using esters of bromo acetic acid as the alkylating agent to perform this transformation. However we choose to investigate a more general method that would allow introduction of groups where the requisite alkylating agent might not be sufficiently activated for use with the enamine procedure. Thus decalone 2 was carbomethoxylated using sodium hydride in dimethyl carbonate to give the β-ketoester 3 in 80% yield (Scheme II). Now the C-3 position was highly activated and could, in principle, be alkylated with a wide variety of alkylating agents. In the present study, methyl bromoacetate was used and the crystalline alkylated product 4 was obtained in 85% yield. Removal of the C-3 carbomethoxy group was accomplished using barium

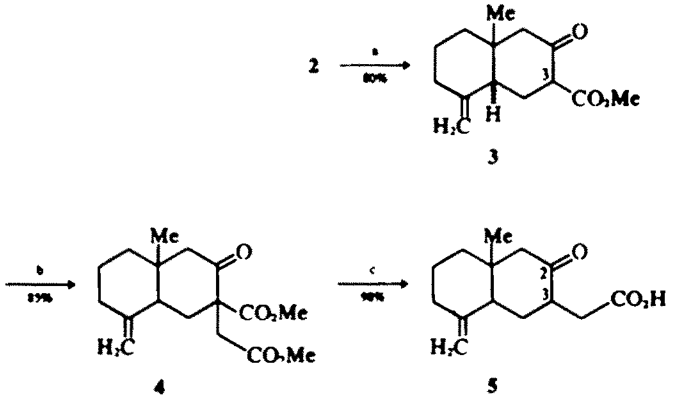


a, NaBH$_4$, MeOH; b, Na, NH$_3$(l.), EtOH; c, Al(i-PrO)$_3$, CH$_3$COCH$_3$, PhCH$_3$; d, Li (CH$_3$)$_2$Cu, Et$_2$O; e, Ph$_3$P = CH$_2$, DMSO; f, H$_3$O$^+$

SCHEME 1.

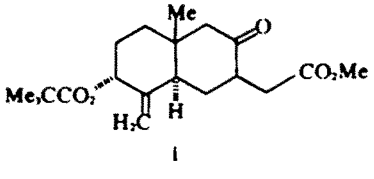
hydroxide octahydrate in refluxing ethanol to give the crystalline ketoacid 5 in 98% yield. This compound had also been prepared by Minato and Horibe[2] but was reported to be an oily ketoacid rather than a crystalline material. Despite this discrepancy, analytical analysis, spectral data and subsequent transformations assured us that the assigned structure was correct. It is important to point out that the overall yield of the 3-step procedure for introduction of the acetic acid side-chain is as good, and in many cases better, than that obtained from enamine alkylation.

The second major feature of the synthesis was the formation of the *cis*-lactone ring by reduction of the ketone function and lactonization. Minato and Horibe[2] had found that direct reduction of the ketoacid 5 with sodium borohydride gave the desired *cis*-lactone 6 in 66% yield. Although it was not stated in the communication, presumably the rest of the reduction mixture had an equatorial alcohol at C-2 which upon lactonization would have yielded the undesired *trans*-lactone.* From this observation it was clear that the angular methyl group was providing some steric hinderance to the incoming hydride at C-2, causing the approach from the opposite side of the molecule to be favored and thus giving a predominance of the axial alcohol prior to lactonization. Thus it was reasoned that a sterically more hindered borohydride reagent should increase the selectivity of the reduction and give more of the desired *cis*-lactone. For this to be realized, of course, the acetic acid side chain at C-3 in ketoacid 5 would have to be equatorial. This was assumed to be the case because under the rigorous conditions of decarboxylation of compound 5 the thermodynamically more stable equatorial orientation would be expected. Indeed it was found that treatment of ketoacid 5 with ethereal diazomethane and reduction of the crude ketoester with K Selectride† gave crystalline *cis*-lactone 6 in 96%



a, NaH, $(OMe)_2CO$; b, NaH, $BrCH_2CO_2Me$, THF; c, $Ba(OH)_2 \cdot 8H_2O$, EtOH, reflux.

SCHEME 2.



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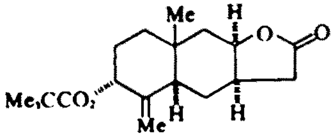

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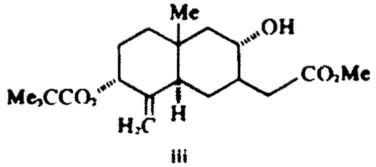

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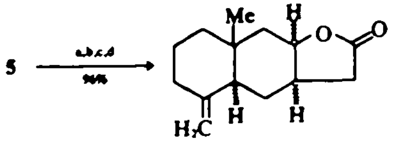
*In a study of the synthesis of a related sesquiterpene, (±)-isotelekin, we observed that reduction of i with sodium borohydride followed by acidic workup gave a 3:1 mixture of ii:iii.

†K Selectride is the Aldrich trade name for potassium tri-sec-butylborohydride. This reagent was first studied by H. C. Brown.[8]

yield after workup. In this case, both the spectral properties and melting point were in good agreement with those of Minato and Horibe. It is important to point out that no detectable amount of reduction giving rise to the equatorial alcohol at C-2 was observed. Also it is important to note that the above reduction only worked well on the ketoester derived from ketoacid 5; attempts at direct reduction of the ketoacid 5 failed to give the desired *cis*-lactone 6.



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a, CH_2N_2, Et_2O; b, K Selectride, THF, −78°; c, H_2O_2, 3 NNaOH; d, H_3O^+

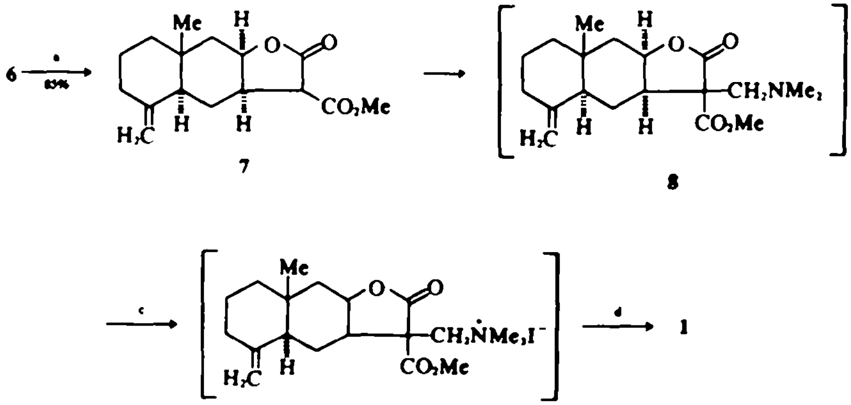
The third major feature of the synthesis of isoalantolactone involved the introduction of the α-methylene group onto the butyrolactone ring. Although Minato and Horibe[2f] had accomplished this, we choose to investigate an alternate procedure. Previously we had developed a mild, efficient method for the synthesis of the α-methylene-γ-butyrolactone group.[21] The application of this sequence to *cis*-lactone 6 yielding racemic isoalantolactone is shown in Scheme III. Carbomethoxylation of compound 6 was carried out in 85% yield using sodium hydride in dimethyl carbonate to give crystalline lactoneester 7. Mannich reaction on compound 7 using formaldehyde and dimethylamine gave the crude Mannich base 8 which was directly quaternized in excess methyl iodide. The resulting quaternary ammonium salt 9 could easily be separated from unreacted lactoneester 7 by trituration with anhydrous ether. Heating the salt 9 in N,N-dimethylformamide at 80° overnight gave crude (±)-isoalantolactone. Chromatography on Florisil gave crystalline (±)-isoalantolactone in 50% conversion based on compound 7 (65% yield based on recovered compound 7). This synthetic product had mp 94–95° in good agreement with that reported by Minato and Horibe[2f] and had superimposable solution IR and NMR spectra with those of natural isoalantolactone.

EXPERIMENTAL

All m.ps are uncorrected. IR spectra were recorded on a Beckman IR-8 spectrophotometer. NMR spectra were recorded on a Varian A-60A instrument. Chemical shifts are quoted in ppm downfield from internal TMS. High resolution mass spectra were obtained with a Varian M-66 spectrometer. Combustion analyses were done by Chemalytics, Inc., Tempe, Arizona. Light petroleum used was reagent grade with boiling range 30-60°. All reactions were carried out under a N_2 atmosphere. Anhyd $NaSO_4$ was used as the drying agent. Florisil (60/100 A) used for chromatography was purchased from Wilshire Chemical Co., Inc.

Ketoester (3). To 360 mg (8·5 mmol) of a 57% mineral oil dispersion of NaH (twice washed with anhyd benzene) in 2 ml of dry Me_2CO_3 was added 890 mg (5 mmol) of 5 2[7] in 8 ml of dry Me_2CO_3. The mixture was refluxed for 4 hr after which it was poured into 50 ml of water, acidified and extracted with ether. The combined ether layers were washed with water and brine, dried and concentrated to give 1·12 g crude product. Elution with 60% light petroleum − 40% dichloromethane from Florisil (30 g) afforded 945 mg (80% yield) of oily 3, which exists mainly in the enol form: IR (neat) 1715 and 1740 (w, keto form), 1660 and 1615 (s, enol form), and 890 cm^{-1} $(\rangle C{=}CH_2)$; NMR (CCl_4) δ 0·75 (s, 3H, angular CH_3), 3·67 (s, 3H, $-OCH_3$), 4·53 (broad s, 1H, vinyl proton), 4·70 (broad s, 1H, vinyl proton), and 11·70 ppm (s, 1H, enolic proton); mass spectrum (*m/e*): Calcd. for $C_{14}H_{20}O_3$: 236·1412. Found: 236·1433.

Ketodiester (4). To 290 mg (6·9 mmol) of a 57% mineral oil dispersion of NaH in 10 ml of dry THF was added



a, NaH, $(OMe)_2CO$; b, CH_2O (37%), Me_2NH, $Me_2NH{\cdot}HCl$ dioxane; c, MeI; d, DMF, 80°C

SCHEME 3.

650 mg (2·75 mmol) of **3** in 10 ml of dry THF. After stirring for 30 min at room temp, 920 mg (6 mmol) methyl bromoacetate was slowly added and the resulting mixture was stirred overnight at 85°. After cooling, the mixture was poured into cold water and extracted 3 times with ether. The combined ether extracts were washed with water and brine, dried and concentrated. The crude product was chromatographed on Florisil (30 g). Elution with 50% light petroleum – 50% dichloromethane afforded 720 mg (85% yield) of crystalline **4**. Recrystallization from an ether-light petroleum mixture gave material with m.p. 111–112°; IR (CCl_4) 1745 (ester C=O), 1715 (ketone C=O), 1640 (C=C), and 895 cm^{-1} $\left(\rangle C{=}CH_2\right)$; NMR ($CDCl_3$) δ 0·77 (s, 3H, angular CH_3), 2·24 (d, 2H, $-C\underline{H}_2CO_2CH_3$), 3·60 (s, 3H, $-OCH_3$), 3·70 (s, 3H, $-OCH_3$), 4·53 (broad s, 1H, vinyl proton), and 4·75 ppm (broad s, 1H, vinyl proton). (Found: C, 66·10; H, 7·93. Calcd. for $C_{17}H_{24}O_5$: C, 66·21; H, 7·84%).

Ketoacid (**5**). To 310 mg (1·0 mmol) of **4** in 4 ml EtOH was added a soln of 1·4 g $Ba(OH)_2$ octahydrate in 10 ml water. The mixture was refluxed for 20 h, cooled, acidified and extracted 3 times with ether. The combined ether extracts were washed with water and brine and dried. Removal of the solvent gave 233 mg (98% yield) of crystalline **5**. An analytical sample was prepared by recrystallization from an ether-light petroleum mixture giving material with m.p. 112·5–113°; IR ($CHCl_3$) 3600–2500 (broad O—H), 1710 (C=O), 1640 (C=C), and 890 cm^{-1} $\left(\rangle C{=}CH_2\right)$; NMR ($CDCl_3$) δ 0·68 (s, 3H, angular CH_3), 4·43 (broad s, 1H, vinyl proton), 4·73 (broad s, 1H, vinyl proton), and 10·10 ppm (s, 1H, $-CO_2\underline{H}$). (Found: C, 70·92; H, 8·62. Calcd. for $C_{14}H_{20}O_3$: C, 71·16; H, 8·53%).

Lactone (**6**). A soln of 300 mg (1·27 mmol) of **5** in 25 ml ether was cooled to 0° and an ethereal soln of diazomethane was added until a yellow color persitsed and N_2 evolution ceased. After warming to room temp, AcOH was added to destroy any excess diazomethane. The ether soln was washed with 5% NaOHaq until basic, water, and brine and dried. Removal of solvent gave 220 mg, quantitative yield, of a ketoester that was used without further purification: IR (neat) 1735 (ester C=O), 1710 (ketone C=O), 1640 (C=C), and 890 cm^{-1} $\left(\rangle C{=}CH_2\right)$; NMR ($CCl_4$) δ 0·67 (s, 3H, angular CH_3), 3·57 (s, 3H, $-OCH_3$), 4·43 (broad s, 1H, vinyl proton), and 4·73 ppm (broad s, 1H, vinyl proton).

The crude ketoester from above was taken up in 8 ml of dry THF and the solution was cooled to – 78°. Slowly, 5·6 ml (2·8 mmol) of K SELECTRIDE (potassium tri-*sec*-butylborohydride, 0·5 M soln in THF, Aldrich Chemical CO.) was added and the mixture was stirred for 3 h. After the addition of 3 ml of 3N NaOH, the mixture was warmed to room temp and 3 ml of 30% H_2O_2 was added. Following the initial exothermic reaction, the soln was stirred an additional 30 min. Then 10 ml of 3N HCl was added and the mixture was stirred 15 min at room temp. After extraction with ether, the combined organic layers were washed with water and brine and dried. Removal of solvent gave 290 mg of crude material that was chromatographed on Florisil (9 g). Elution with 50% light petroleum – 50% dichloromethane afforded 270 mg (96% yield) of crystalline **6**. Recrystallization from an ether-light petroleum mixture gave material with m.p. 105–107° (lit[21] m.p. 103–105°C); IR (CCl_4) 1170 (C=O), 1645 (C=C), and 890 and 900 cm^{-1} $\left(\rangle C{=}CH_2\right)$; NMR ($CCl_4$) δ 0·82 (s, 3H, angular CH_3), 4·43 (m, 2H, $-C\underline{H}-O$ and vinyl proton), and 4·70 ppm (broad s, 1H, vinyl proton).

Lactoneester (**7**). To 110 mg (2·6 mmol) of a 57% mineral oil dispersion of NaH (twice washed with anhyd benzene) in 2 ml of dry Me_2CO_3 was added 220 mg (1·0 mmol) of **6** in 5 ml of dry Me_2CO_3. The mixture was refluxed for 10 h after which it was poured into 50 ml water, acidified and extracted with ether. The combined ether layers were washed with water and brine, dried and concentrated to give 280 mg crude product which was chromatographed on Florisil (9 g). Elution with 40% light petroleum – 60% dichloromethane afforded 235 mg (85% yield) of crystalline **7**. Recrystallization from an ether-light petroleum mixture gave material with m.p. 97–99°; IR (CCl_4) 1775 (lactone C=O), 1735 (ester C=O), 1645 (C=C), and 890 cm^{-1} ($C{=}CH_2$); NMR (CCl_4), δ 0·81 (s, 3H, angular CH_3), 3·25 (s, 1H, $O{=}C{-}\overset{|}{C}\underline{H}{-}CO_2CH_3$), 3·70 (s, 3H, OCH_3), 4·42 (broad s, 1H, vinyl proton), and 4·70 (m, 2H, $-C\underline{H}-O$ and vinyl proton). (Found: C, 68·83; H, 8·12. Calcd. for $C_{16}H_{22}O_4$: C, 69·04; H, 7·97%).

(±)-*Isoalantolactone* (**1**). To 2 ml dioxane was added 0·07 ml (~1 mmol) dimethylamine, 82 mg (~1 mmol) dimethylamine hydrochloride and 0·13 ml (~1 mmol) 37% aqueous formaldehyde. To this mixture was added 65 mg (0·23 mmol) of **7** and the soln was stirred for 12 h at room temp. After the addition of 15 ml 3N NaOH, the soln was extracted 3 times with ether. The combined ether layers were washed with water and brine, dried and concentrated to give the crude **8** as an oily liquid that was used in the following reaction without further purification.

The crude base **8** from above was stirred in 3 ml MeI for 12 h at room temp. Excess MeI was removed *in vacuo* and the crystalline quaternary salt **9** was triturated with ether. Evaporation of the ether washings gave 14 mg unreacted **7**. The yield of **9** was 57 mg.

The crystalline **9** from above was taken up in 5 ml dry N,N-dimethylformamide and was heated for 16 h at 80°. After cooling, water was added and the mixture was extracted 3 times with ether. The combined ether layers were washed with water and brine, dried and concentrated to give 27 mg of a crude product that was chromatographed on Florisil (2 g). Elution with 75% light petroleum – 25% dichloromethane afforded 27 mg (50% conversion based on **7** or 65% yield based on recovered **7**) of crystalline (±)-isoalantolactone. Recrystallization from an ether-light petroleum mixture gave material with m.p. 94–95° (lit[21] m.p. 93–94°). The synthetic material was found to have identical solution IR and NMR spectra to an authentic sample of natural isoalantolactone: IR (CCl_4) 3090(s), 3000(m), 2980(m), 2950(s), 2880(m), 2850(m), 1765(s), 1665(w), 1645(m), 1450(m), 1440(m), 1410(m), 1385(m), 1370(m), 1355(m), 1345(m), 1330(m), 1310(m), 1295(m), 1280(w), 1260(s), 1200(m), 1180(m), 1160(m), 1135(s), 1100(s), 1040(m), 965(m), 940(s), 890(s), 680(w), and 640 cm^{-1}(m); NMR (CCl_4) δ 0·82 (s, 3H, angular CH_3), 1·0–3·3 (complex, 12H), 4·37 (m, 2H, $-C\underline{H}-O$ and vinyl proton), 4·67 (broad s, 1H, vinyl proton), 5·43 (s, 1H, vinyl proton) and 5·90 ppm (s, 1H, vinyl proton).

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