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AN IMPROVED SYNTHESIS OF (±)-METHYL SHIKIMATE THROUGH STEREOSELECTIVE CIS-DIHYDROXYLATION OF (±)-METHYL 5β-HYDROXYCYCLOHEXA-1,3-DIENOATE UNDER PRÉVOST'S REACTION CONDITIONS

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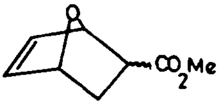
Abstract A Prévost-type reaction under "wet" conditions upon the O-^{t}butyldimethylsilyl derivative of (±)-methyl 5β-hydroxycyclohexa-1,3-dienoate gives (±)-methyl 3α-acetoxy-4β-hydroxy-5β-^{t}butyldimethylsilyloxycyclohexene which may be readily deprotected to afford (±)-methyl shikimate in very high yield. Less selectivity is observed in a similar reaction upon the parent alcohol and when this compound is reacted under dry conditions the major product is (±)-methyl 4β,5β-epoxy-3β-acetoxycyclohexenoate. An analysis of Prévost reactions with exo and endo methyl 7-oxabicyclo [2,2,1]hept-5-en-2-oate is also described.

Recently we reported[1] a brief synthesis of (±)-methyl shikimate (4) through the stereocontrolled base promoted [$Li(Me_3Si)_2N$] ring-opening of the 7-oxabicyclo[2,2,1]heptene (1),[2] followed by cis-dihydroxylation [OsO_4] of the product diene alcohol (2), protected as the TBDMS derivative (3). A closely similar synthesis has recently been described by Rodrigo et al.[3]



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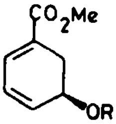
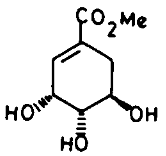


2, R:H
3, R:t-BuMe$_2$Si



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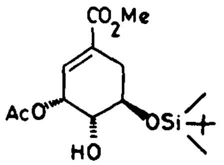
We now record that when the O-silyl ether (3) is heated with iodine, silver acetate and acetic acid containing water (1eq.) a hydroxy acetate (5)[#] is obtained in >80% yield. This product may then be deacetylated and desilylated to give (±)-methyl shikimate. Since the deprotection steps are virtually quantitative the overall yield (26%) from the adduct (1) is similar to that afforded by the osmylation technique we have already described,[1] but in practice this new procedure is far more convenient and much less time consuming.

Previously we predicted and observed the large TBDMS group in the ether (3) to direct osmylation to the less crowded α-face of the diene system. However, in the present study should the normal mechanism[4] of the Prévost reaction prevail, iodination at the Δ^3-bond must occur preferentially syn to the β-orientated silyloxy group giving the intermediate iodinium species (6). Since the hydroxyacetate (5) is the only isolable product participation of the expected α-iodinium cation (7) is ruled out.

[#] Chemical shift data and coupling constants almost identical to those for shikimic acid and its triacetate.

An alternative mechanism is possible. Thus Michael addition of acetate ion from the α-face at C-4 perhaps mediated by the silver cation, may preceed electrophilic attack of iodine at C-3[(8)→(9)]. Eventually this would lead to the same acetoxonium ion (10) as that expected from the typical Prévost reaction. It is interesting, however, that only one hydroxyacetate is obtained from the ring-opening of this assumed intermediate for in a similar reaction upon the free alcohol (2) much less selectivity is observed and <u>seven</u> products are obtained. These are: (±)-methyl 3α-acetoxy-4α,5β-dihydroxycyclohexenoate (12) and (±)-methyl 4α-acetoxy-3α,5β-dihydroxycyclohexenoate (11) (ratio 2.5:1, yield 28.5%), (±)-methyl 4α-acetoxy-5β-hydroxy-3β-iodocyclohexenoate (13) and (±)-methyl 4β-acetoxy-5β-hydroxy-3α-iodocyclohexenoate (14) (ratio 4:1, yield 8.4%), (±)-methyl 3β-acetoxy-5β-hydroxy-4α-iodocyclohexenoate (15) and (±)-methyl 3α-acetoxy-5β-hydroxy-4β-iodocyclohexenoate (16) (ratio 5:1, yield 6.7%) and methyl 3-hydroxybenzoate, (13%). Each binary mixture was separated by flash chromatography and the individual structures determined by ^{13}C and ^{1}H NMR spectroscopy.



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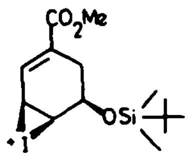

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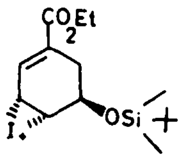

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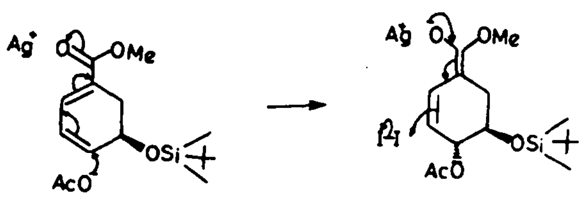

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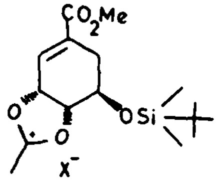

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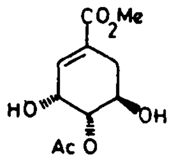

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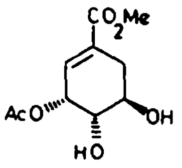

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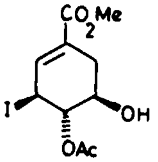

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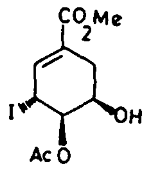

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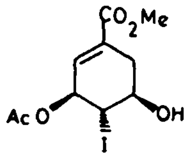

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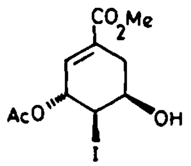

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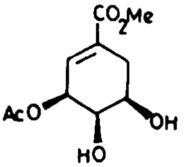
A longer reaction time (>11h) resulted in further reaction of the iodoacetates in the product, but the alternative hydroxyacetates (17) and (18) were not detected. Instead the epoxide (19) was generated, and it is noteworthy that when the mixed iodoacetates (15) and (16) were allowed to stand in chloroform solution the isomer (15) decomposed into this epoxide. Deacetylation of the epoxide afforded the known structure (20) previously obtained by Berchtold[6] by the reaction of methyl shikimate with diethyl azodicarboxylate-triphenylphosphine. Surprisingly, the epoxide (19) is the major reaction product (yield 34%) when the alcohol is reacted with iodine and silver acetate in carbon tetrachloride. The only other compound isolated from this reaction is methyl 3-hydroxybenzoate (yield 12%).



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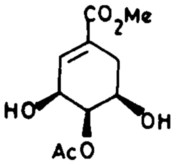

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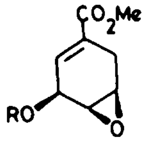
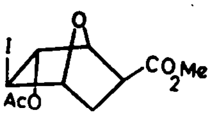


19, R=Ac
20, R=H

Reaction of the mixed *exo*- and *endo* adducts (1) under "dry" Prévost's conditions (I_2, AgOAc, HOAc) afforded 70% of the two *exo*- iodoacetates (21) and (22) (ratio 1:1) and the known iodolactone (23) (24% yield).[7] The alternative endo-iodoacetates (24) and (25) were not detected, thus it is possible that the iodinium species (26) undergoes intra-molecular attack by the α-orientated ester group more rapidly than intermolecular reaction with acetate ion. However, we also note that if water (1eq) is added to the reagents the proportion of the iodolactone in the products is increased to 60%, which may imply that more than one mechanism may operate to give this product.



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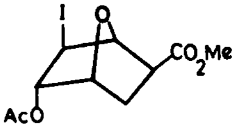

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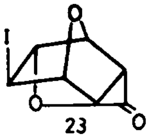

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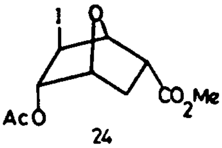

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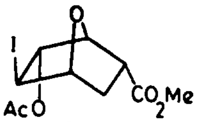

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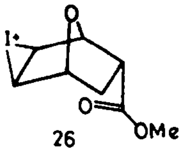

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These studies therefore extend and complement recent work in this area and indicate interesting and subtle differences in osmylation and Prévost reactions with hydroxycyclohexadienes and their derivatives.[1,3,8]

ACKNOWLEDGEMENT

We thank O.W. Howarth, University of Warwick, High Field N.M.R. Service, for recording spectra and for helpful advice.

EXPERIMENTAL

All m.p. are corrected. ^1H N.M.R. spectra were recorded at 100 or 400 MHz and ^{13}C N.M.R. spectra at 22.5MHz; chemical shifts were measured downfield relative to tetramethylsilane as internal standard except for those compounds bearing a O-t-butyldimethylsilyl group. Here chloroform was used as internal standard.

(±)-Methyl 5-β-O-t-butyldimethylsilyloxycyclohexa-1,3-dienoate (3) t-Butyldimethylsilyltriflate ($0.7cm^3$, 3mmol) was added to 2,6-lutidine ($0.5cm^3$, 4.3mmol) at 0°C and the mixture was stirred for 30 minutes. The hydroxy diene (2), (0.31g, 2mmol) in dichloromethane ($2cm^3$) was then slowly introduced and the mixture stirred for a further 30 minutes. After this time, t.l.c. analysis showed that all the hydroxydiene had reacted to give a single product (Rf 0.77, SiO_2, 30% ethyl acetate in 60-80°C petrol). The reaction mixture was poured onto ice and saturated aqueous sodium hydrogen carbonate and extracted with dichloromethane ($3x15cm^3$). The dry, combined extracts were then evaporated to yield the O-silyl derivative (3) as an oil which was purified by chromatography on a short-path silica column eluting with 30% ethyl acetate in 60-80°C petrol Yield 0.51g, 95%; λ_{max} 272nm; $\nu_{max}(CHCl_3)$ $1710cm^{-1}$; $\delta_H(CDCl_3)$ 0.20 (s, 6H, $(C\underline{H}_3)_2Si$), 0.91(s,9H, $(C\underline{H}_3)_3CSi$), 2.62(2xdd, 2H, $\underline{J}_{6,5}$=8Hz, $\underline{J}_{6,2}$=3Hz, H_2-6), 3.68(s,3H,$OC\underline{H}_3$), 4.45(bt, 1H,H-5), 5.95(m, 2H,H-3,H-4), 6.86(m,1H,H-2); $\delta_C(CDCl_3)$-4.56 (3xq, $(\underline{C}H_3)_3CSi$), 18.2(s,$(CH_3)_3CSi$), 25.9(2xq, $(CH_3)_2Si$), 31.6(t,C-6), 51.6(q,$O\underline{C}H_3$), 65.5(d,C-5), 123.6(s), 127.4(s), 128.4(s),129.6(d,C-4), 131.9(d, C-3), 132.9(d,C-2), 135.8(s,C-1), 167.5(s,$\underline{C}$=O). $\underline{m/z}$ (EI) 268(M^+, 2%), 253(3.4%), 211(49%), 105(100%), 75(90%). This compound was used directly in the next step.

Prévost reaction upon (±)-methyl 5-β-O-t-butyldimethylsilyloxycyclohexa-1,3-dienoate (3) under:

"Wet" conditons: A mixture of silver acetate (0.5g, 3mmol) and iodine (0.38g, 1.5mmol) in glacial acetic acid ($15cm^3$) was stirred at ambient temperature and when all iodine was consumed, the O-silyl derivative (3) (0.4g, 1.5mmol) in glacial acetic acid ($8cm^3$) was introduced. The reaction mixture was heated at 70°C for a further two hours before glacial acetic acid containing water (53.6μl) was added. The mixture was then heated for further 9 hours and a yellow precipitate (AgI) which had formed was filtered off, and washed with chloroform. Glacial acetic acid was removed from the filtrate by evaporation under reduced pressure and the residue was extracted with chloroform and the extracts dried ($MgSO_4$). Evaporation of the combined extracts under reduced pressure gave a brown oil, the t.l.c. analysis of which showed only one component to be present. Chromatography on a short-path silica column, eluting with 40% ethyl acetate in 60-80°C petrol afforded (±)-methyl 3α-acetoxy-4β-hydroxy-5β-t-butyldimethylsilyloxycyclohexene (5) (0.41g, 80%) as a yellow oil· ν_{max} (liq.film) 3150, ∿$1725cm^{-1}$; $\delta_H(CDCl_3)$ 0.15(s,6H,$(C\underline{H}_3)_2Si$), 0.95(s,9H,$(C\underline{H}_3)_3CSi$), 2.20(s,3H,$COC\underline{H}_3$) 2.30(m,1H,H-6β), 2.83(m,1H,H-6α), 3.75(s,3H,CO_2CH_3), 3.93(m, 1H, H-5), 4.19(m,1H,H-4), 5.70(m,1H,H-3), 6.76(m,1H,H-2); $\delta_C(CDCl_3)$ -4.76(2xq,$(\underline{C}H_3)_2Si$) -4.98(q), 17.4(s,$(CH_3)_3\underline{C}Si$), 20.9(q,$CO\underline{C}H_3$), 30.8(t,C-6), 51.3(q,CO_2CH_3), 68.3(d,C-3), 69.1(d,C-4), 69.8(d,C-5), 131.0(s,C-1), 133.1(d,C-2), 166.5(s,$\underline{C}O_2CH_3$). $\underline{m/z}$ (CI) 345(M+1, 63%), 327(22%), 285(63%).

(±)-Methyl shikimate. (±)-Methyl 3α-acetoxy-5β-t-butyldimethylsilyloxy-4β-hydroxycyclohexenoate (5) (0.12g, 0.35mmol) in methanol ($5cm^3$) was stirred in aqueous ammonia (2N, $1cm^3$) until all the starting material had been consumed (∿2hours). Methanol was then removed under reduced pressure to give a colourless oil (0.11g) (Rf 0.30, SiO_2, 40% ethyl acetate in 60-80°C petrol). The physical data for this product were identical with those obtained previously[1] for (±)-methyl 5β-O-t-butyldimethylsilylshikimate. It was then converted into (±)-methyl shikimate as before. This product was identical in every respect with (±)-methyl shikimate,[1] but as an extra proof of structure a sample (0.09g) was reacted with acetic anhydride (0.14cm^3) and pyridine (0.14cm^3) at room-temperature (3hours) to give the triacetyl derivative of (±)-methyl shikimate (R_f 0.35, SiO_2, 40% ethyl acetate in 60-80°C petrol); ν_{max} (liq.film) br. 1725cm^{-1}; δ_H($CDCl_3$) 2.03, 2.05, 2.07 (3s, 9H, 3xCOC$\underline{H}_3$), 2.47(m,1H,$\underline{J}_{gem}$=18.6Hz, $\underline{J}_{6\beta,5}$=5Hz, $\underline{J}_{6\beta,2}$=1.6Hz, H-6β), 2.95(m,1H,$\underline{J}_{gem}$=18.6Hz, $\underline{J}_{6\alpha,5}$=5.6Hz, $\underline{J}_{6\alpha,2}$=1.6Hz, $\underline{J}_{6\alpha,3}$=1.8Hz, H-6α), 3.75(s,3H,OC$\underline{H}_3$), 5.22(m,1H,$\underline{J}_{4,5}$=8Hz, $\underline{J}_{4,3}$=4Hz,H-4), 5.27(m,1H,$\underline{J}_{5,4}$=8Hz, $\underline{J}_{5,6\beta}$=5Hz, $\underline{J}_{5,6\alpha}$=5.6Hz, H-5), 5.73(m,1H,$\underline{J}_{3,4}$=4Hz, $\underline{J}_{3,2}$=4Hz, $\underline{J}_{3,6\alpha}$=1.8Hz, H-3), 6.76(m,1H,$\underline{J}_{2,3}$=4Hz, $\underline{J}_{2,6\alpha}$=1.6Hz, $\underline{J}_{2,6\beta}$=1.6Hz, H-2); δ_C($CDCl_3$) 2x20.7(2xq, CO$\underline{C}H_3$), 20.9(q,CO$\underline{C}H_3$), 28.6(t,C-6), 52.5(q,O$\underline{C}H_3$), 66.0(d,C-5), 66.8(d,C-4), 67.8(d,C-3), 131.3(s,C-1), 132.7(d,C-2), 165.9(q,$\underline{C}O_2CH_3$), 2x169.8(s,$\underline{C}OCH_3$), 169.9(s, $\underline{C}OCH_3$); *m/z* (EI) 254(100%), 152(76%), 43(49%), (CI) 314(M$^+$,2%), 255(14%), 115(5%) [Found: C,53.5; H,5.9 Calc. for $C_{14}H_{18}O_8$: C, 53.8; H,5.7%].

Prévost reaction on (±)-methyl 5β-hydroxycyclohexa-1,3-dienoate (2) under: (a) "Wet" conditions

A mixture of silver acetate (0.87g, 5.2mmol) and iodine (0.66g, 2.6mmol) in glacial acetic acid (20cm^3) was stirred at room temperature until all the iodine was consumed. The hydroxydiene (2) (0.54g 3.5mmol) in glacial (10cm^3) was then introduced and the reaction mixture heated at 70°C for two hours before glacial acetic acid (2cm^3) containing distilled water (50µl) was added. The mixture was then heated at 70°C for a further 9 hours, after which time a yellow precipitate (AgI) was filtered off and washed with chloroform (5cm^3). Acetic acid was removed from the filtrate by evaporation *in vacuo* and the crude residue was extracted into chloroform. Removal of the chloroform gave a yellow oil. The t.l.c. analysis (SiO_2) indicated the presence of four components (R_f 0.65, 0.40 in 30% ethyl acetate in 60-80°C petrol and 0.37 and 0.38 in ethyl-acetate). The crude product was chromatographed on silica (60g) using 30% ethyl acetate in 60-80°C petrol as eluant to remove the first two components and then using 50% ethyl acetate in 60-80°C petrol to elute the last two. These products proved to be (in order of elution): (i) *Methyl 3-hydroxybenzoate* (0.05g, 13%) as colourless prisms, m.p. 69°C (lit.,[9] 69°C); λ_{max}280, 342, 370 nm; ν_{max}($CHCl_3$) br. 3310, 1750cm^{-1}; δ_H($CDCl_3$) 3.92(s,3H,OC$\underline{H}_3$), 7.02-7.62(m,4H,H_2-H_6); *m/z* (EI) 152(M+,49%), 121(100%), 93(44%).

(ii) *(±)-Methyl 3β-acetoxy-4β,5β-epoxycyclohexenoate (19)* (0.1g, 11.3%), as a yellow oil; ν_{max}(CCl_4) 1750cm^{-1}; δ_H($CDCl_3$) 2.18(s,3H,OCOC$\underline{H}_3$), 2.50(m,1H,H-6β), 3.15(s,3H,$CO_2C\underline{H}_3$), 3.50 (m,1H,H-4), 3.50(m,1H,H-5), 3.75(s,3H,OC$\underline{H}_3$), 5.79(m,1H,H-3), 6.50(m,1H,H-2); δ_C($CDCl_3$) 20.9(q, CO$\underline{C}H_3$), 24.4(t,C-6), 50.7(d,C-4), 52.1(q,$CO_2\underline{C}H_3$), 52.1(d,C-5), 68.1(d,C-3), 128.2(s,C-1), 132.4(d,C-2), 166(s,$\underline{C}O_2CH_3$), 170.4(s,O$\underline{C}OCH_3$); *m/z* (CI) 213(M+1, 3%), 197(1%), 137(46%).

(iii) *A mixture of (±)-methyl 3α-acetoxy-4α,5β-dihydroxycyclohexenoate (12) and (±)-methyl 4α-acetoxy-3α,5β-dihydroxycyclohexenoate* (11) (ratio 2.5:1, 0.2g, 59.8%) as a yellow oil; ν_{max}3420, br 1720cm^{-1}; *m/z* (CI) 171 (22%), 153(57%), 139(75%); *m/z* (EI) 212(0.3%), 198(1%), 170(22%). Data for compound (12) δ_H($CDCl_3$), 2.07(s,3H,OC$\underline{H}_3$), 2.25(m,1H,$\underline{J}_{gem}$=19.2Hz, $\underline{J}_{6\beta,5}$=1.6Hz, H-6β), 2.90(m,1H,$\underline{J}_{gem}$=19.2Hz, $\underline{J}_{6\alpha,5}$=6Hz, $\underline{J}_{6\alpha,2}$=1.2Hz, H-6α), 3.73(s,3H,$CO_2C\underline{H}_3$), 3.98(m,1H,$\underline{J}_{5,4}$= 9.2Hz, $\underline{J}_{5,6\beta}$=5.6Hz, $\underline{J}_{5,6\alpha}$=6Hz, H-5), 5.58(t,1H,$\underline{J}_{3,4}$= 4.6Hz, $\underline{J}_{3,2}$=2.4Hz,H-3), 6.75(m,1H,$\underline{J}_{2,3}$= 2.4Hz, $\underline{J}_{2,6\alpha}$=1.2Hz, $\underline{J}_{2,6\beta}$=1.6Hz,H-2); δ_C($CDCl_3$) 21.0(q,CO$\underline{C}H_3$), 31.9(t,C-6), 52.2(q,$CO_2\underline{C}H_3$), 67.1(d,C-5), 68.5(d,C-4), 70.6(d,C-3), 132.3(s,C-1), 136.3(d,C-2), 166.4(s,$\underline{C}O_2CH_3$), 170.8(s, $\underline{C}OCH_3$). Data for compound (11) δ_H($CDCl_3$) 2.10(s,3H,COC$\underline{H}_3$), 2.32(m,1H,$\underline{J}_{gem}$=18.8Hz, $\underline{J}_{6\beta,5}$=5.8Hz, $\underline{J}_{6\beta,2}$=2Hz,H-6β), 2.74(m,1H,$\underline{J}_{gem}$= 18.8Hz, $\underline{J}_{6\alpha,5}$=5.8Hz, $\underline{J}_{6\alpha,2}$=1.6Hz, $\underline{J}_{6\alpha,\beta}$=2Hz, H-6α), 3.70(s,3H, CO_2CH_3), 4.20(qd,1H,$\underline{J}_{5,4}$=7.6Hz, $\underline{J}_{5,6\alpha}$= 5.8Hz, $\underline{J}_{5,6\beta}$=5.8Hz, H-5), 4.63(m,1H,$\underline{J}_{3,4}$=4Hz, $\underline{J}_{3,2}$=3.6Hz, $\underline{J}_{3,6\alpha}$=2Hz, H-3), 4.94(dd,1H,$\underline{J}_{4,5}$=7.6Hz, $\underline{J}_{4,3}$=4Hz,H-4), 6.81(m,1H,$\underline{J}_{2,3}$=3.6Hz, $\underline{J}_{2,6\beta}$=2Hz, $\underline{J}_{2,6\alpha}$=1.6Hz, H-2); δ_C($CDCl_3$) 21.1(q,CO$\underline{C}H_3$), 31.1(t,C-6), 52.2(q,$CO_2\underline{C}H_3$), 64.9(d,C-3), 67.1(d,C-5), 71.6(d,C-3), 132.9(s,C-1), 136.8(d,C-2), 166.2(s,$\underline{C}O_2CH_3$), 171.2(s,$\underline{C}OCH_3$).

Attempts were not made to separate the two hydroxyacetates since on hydrolysis they both afford (±)-methyl shikimate.

(b) *"Wet" conditions but rather more mild conditions than above.* A mixture of silver acetate (1.17g, 7mmol) and iodine (0.89g, 3.5mmol) in glacial acetic acid (30cm^3) was stirred at ambient temperature and when all iodine was consumed, the hydroxydiene (2) (0.54g, 3.5mmol) in glacial acetic acid (20cm^3) was introduced. The reaction mixture was then heated at 50°C, before glacial acetic acid (4cm^3) containing water (63μl) was added. The mixture was heated at 50°C for a further 5 hours, the yellow precipitate (AgI) which had formed was filtered off and washed with chloroform. Acetic acid was removed from the filtrate under reduced pressure and the crude residue was extracted into chloroform. The solution was dried (MgSO$_4$) and evaporated to afford a yellow residue. The t.l.c. analysis of this residue showed five components to be present R_f0.65, 0.38, 0.35, 0.15 and 0.14 (SiO$_2$, 30% ethyl acetate / 60-80°C petrol). However, seven products were observed when the t.l.c. analysis was carried out on a long plate with multiple elutions of 15% ethyl acetate in 60-80°C petrol. Preparative chromatography on the Chromatotron (2mm, SiO$_2$ plate, 6cm^3/min, 15% ethyl acetate in 60-50°C petrol) afforded firstly methyl 3-hydroxybenzoate (0.06g, 11.3%). Further elution gave an isomeric mixture of the iodoacetates(13) and (14) (4:1 ratio, 0.1g, 8.4%) as a yellow oil continued elution yielded the iodoacetates(15) and (16)(5:1 ratio, 0.08g, 6.7%). The final products were the hydroxy acetates (12) and (11) (2.5:1 ratio, 0.23g, 28.5%, a colourless oil).

Physical data for the products:

(i) (±)-Methyl 4α-acetoxy-5β-hydroxy-3β-iodocyclohexenoate (13) ν_{max} 3500, br 1750cm^{-1}; δ_H(CDCl$_3$) 2.10(s,3H,COC$\underline{H}_3$), 2.51(dq, 1H,$\underline{J}$gem=18.8Hz, $\underline{J}_{6\beta,5}$=4.8Hz, $\underline{J}$=2.4Hz, H-6β), 3.04(dd,1H, $\underline{J}_{gem}$=18.8Hz, $\underline{J}_{6\alpha,2}$=1.7Hz, H-6α), 3.48(dq,1H,$\underline{J}_{5,6\beta}$=4.8Hz, $\underline{J}_{5,4}$=2.4Hz, H-5), 3.53(dq,1H,$\underline{J}_{3,4}$=2.4Hz, H-3), 3.70(s,3H,CO$_2$CH$_3$), 5.74(qd,1H,$\underline{J}_{4,5}$=2.4Hz,$\underline{J}_{4,3}$=2.4Hz,H-4), 6.56(dq,1H,$\underline{J}_{2,3}$=3.2Hz, $\underline{J}_{2,6\alpha}$= 1.7Hz,H-2); δ_C(CDCl$_3$), 20.9(q,COC$\underline{H}_3$), 24.5(t,C-6), 50.7(d,C-3), 52.1(q,CO$_2\underline{C}$H$_3$), 52.1(d,C-4), 68.2(d,C-5), 128.2(s,C-1), 132.4(d,C-2), 166.2(s,$\underline{C}$O$_2$CH$_3$), 170.5(s,$\underline{C}$OCH$_3$).

(ii) (±)-Methyl 4β-acetoxy-5β-hydroxy-3α-iodocyclohexenoate (14) ν_{max}3500, br 1750cm^{-1}; δ_H(CDCl$_3$), 2.11(s,3H,COC$\underline{H}_3$), 2.33(m,1H,$\underline{J}_{gem}$=17Hz, $\underline{J}_{6\beta,5}$=8.8Hz,H-6β), 2.95(dd,1H,$\underline{J}_{gem}$=17Hz, $\underline{J}_{6\alpha,5}$=4.8Hz, H-6α), 3.73(s,3H,CO$_2$C$\underline{H}_3$), 4.0(m,1H,$\underline{J}_{3,4}$=2.4Hz, H-3), 4.10(dd,1H,$\underline{J}_{5,6\beta}$=8.8Hz, $\underline{J}_{5,6\alpha}$=4.8Hz, H-5), 5.78(m,1H,$\underline{J}_{4,5}$=6.4Hz,$\underline{J}_{4,3}$=2.4Hz,H-4), 6.51(m,1H,$\underline{J}_{2,3}$=2.5Hz, H-2); $\underline{m/z}$ (EI) for isomeric mixture 213 (3%), 195(1.4%), 181(3%), 153(100%).

(iii) (±)-Methyl 3β-acetoxy-5β-hydroxy-4α-iodocyclohexenoate (15) ν_{max}3500, br 1750cm^{-1}; δ_H(CDCl$_3$) 2.18(s,3H,COC$\underline{H}_3$), 2.34(s,1H,O$\underline{H}$ - removed on addition of D$_2$O), 2.46(m,1H,$\underline{J}_{gem}$=17.6Hz, $\underline{J}$=4.8Hz, $\underline{J}_{6\alpha,2}$=1.6Hz, H-6α), 3.82(m,1H,$\underline{J}_{5,6}$=9.2Hz, $\underline{J}$=4.8Hz, H-5), 3.78(s,3H,CO$_2$C$\underline{H}_3$), 4.40(m, 1H,$\underline{J}_{4,5}$=5.2Hz, H-4), 5.85(m,1H,$\underline{J}_{3,4}$=4Hz, H-3), 6.75(m,1H,$\underline{J}_{2,3}$=2.4Hz, $\underline{J}_{2,6\alpha}$=1.6Hz, H-2); δ_C(CDCl$_3$) 20.8(q,CO$\underline{C}H_3$), 31.5(t,C-6), 36.7(d,C-4), 52.5(q,CO$_2\underline{C}$H$_3$), 67.5(d,C-5), 73.1(d,C-3), 131.8(d,C-2), 131.8(d,C-1), 166.2(s,$\underline{C}$O$_2$CH$_3$), 169.6(s,$\underline{C}$OCH$_3$).

(iv) (±)-Methyl 3α-acetoxy-5β-hydroxy-4β-iodocyclohexenoate (16) ν_{max}3500, br 1750cm^{-1}; δ_H(CDCl$_3$) 2.16(s,3H,$\underline{C}$OCH$_3$), 2.35(m,1H,$\underline{J}_{gem}$=17Hz, $\underline{J}$=6Hz, H-6β), 3.05(m,1H,$\underline{J}_{gem}$=17Hz, $\underline{J}$=8Hz, H-6α), 3.76(s,3H,CO$_2$C$\underline{H}_3$), 4.05(m,1H,$\underline{J}_{4,5}$=9.6Hz, H-4), 4.16(m,1H,$\underline{J}_{5,6}$=6Hz,H-5), 5.80(m,1H,$\underline{J}_{3,4}$=4.8Hz, H-3), 6.56(m,1H,$\underline{J}_{2,3}$=2.8Hz, $\underline{J}_{2,6}$=2.5Hz, H-2); δ_C(CDCl$_3$), 20.9(q,COC$\underline{H}_3$), 24.4(t,C-6), 31.7(d,C-4), 53.1(q,CO$_2\underline{C}$H$_3$), 69(d,C-4), 74.8(d,C-3), 130.7(d,C-3), 133.9(s-C-1), 166(s,$\underline{C}$O$_2$CH$_3$), 169.5(s,$\underline{C}$OCH$_3$).

(c) "Dry" conditions

A mixture of silver acetate (1.2g, 7mmol) and iodine (0.38g, 1.5mmol) in dry carbon tetrachloride (15cm^3) was stirred at room temperature until all the iodine was consumed. The hydroxy diene (2) (0.53g, 3.4mmol) in dry carbon tetrachloride (5cm^3) was then introduced and the reaction mixture was heated at 70°C for 11 hours. After this time a yellow precipitate (AgI) which had formed was filtered off and washed with chloroform (5cm^3). The filtrate was dried (MgSO$_4$) and evaporated to give a yellow residue, t.l.c. analysis of which showed the presence of two components with R_f0.65, 0.41 and base-line material (SiO$_2$,30% ethyl acetate in 60-80°C petrol). Preparative chromatography on silica (60g, eluant 30% ethyl acetate in 60-80°C petrol) afforded firstly methyl 3-hydroxybenzoate (0.06g, 12%) as a white solid. Further elution gave the epoxide (19) (0.25g, 34.3%), as a yellow oil. The same reaction was also carried out in "dry" acetic acid and the crude product was analysed in the same way. This indicated a very complex mixture with at least five components and a base-line material. This mixture was not investigated further.

(±)-Methyl 4β,5β-epoxy-3β-hydroxycyclohexenoate (20) The epoxide (19) (0.03g, 0.14mmol) was stirred in aqueous ammonia (2N,0.5cm^3) until t.l.c. analysis showed that the starting material had been consumed (2hours). Methanol was then removed under reduced pressure to give a colourless oil (23mg, 96%), which crystallized on standing, m.p. 81°C (EtOH/60-80°C petrol) (lit.,[6] 81-82°C); ν_{max}(CHCl$_3$) 3560, 3400, 2920, 1710, 1650cm^{-1}; δ_H(CDCl$_3$) 2.40 (brs, 1H, O*H*, this signal is exchanged with D$_2$O), 2.50(m,H,*J*$_{gem}$=20Hz, H-6β), 3.01(m,1H,*J*$_{gem}$=20Hz, H-6α), 3.55(brs,2H,H-4,H-5), 3.72(s,3H,OC*H*$_3$), 4.55(m,1H,H-3), 6.70(brs, 1H, H-2); δ_C(CDCl$_3$), 24.3(t,C-6), 52.1(d,C-4), 52.1(q,CO$_2$*C*H$_3$), 54.6(d,C-5), 65.5(d,C-3), 126.6(s,C-1), 136.0(d,C-2), 166.6(s,*C*O$_2$CH$_3$); *m/z* (C.I., isobutane) 171(M+1), 2.4%), 153(100%); *m/z* (EI) 169(M-1,3%), 155(30%), 138(61%), 111(100%), 81(61%), 53(85%), 39(63%).

Prevost reaction upon endo- and exo- 2-methoxycarbonyl-7-oxabicyclo[2.2.1]hept-5-enes (1) under:

(a) **"Dry" conditions** A mixture of silver acetate (4.7g, 28mmol) and iodine (3.6g, 14mmol) in glacial acetic acid (50cm^3) was stirred at ambient temperature under an atmosphere of nitrogen. When all the iodine had been consumed the adducts (1) (2.1g, 14mmol) in glacial acetic acid (20cm^3) were added. The mixture was then heated at 100°C for 5 hours and a yellow precipitate (AgI) which formed was filtered off and washed with chloroform (10cm^3). Evaporation of the filtrate *in vacuo* gave a white solid, the t.l.c. analysis of which (SiO$_2$: 15% ethyl acetate in 60-80°C petrol) showed three products to be present (R$_f$ 0.40, 0.34 and 0.33). This material was then subjected to preparative chromatography on a Chromatotron (2mm silica plate, eluting with 15% ethyl acetate in 60-80°C petrol, drop rate 6cm^3/min) to afford the iodolactone (23) (0.87g, 24%) and a mixture of the *exo* iodoacetates (21) and (22) (ratio 1:1, 3.3g, 70%) as colourless crystals. Further chromatography of the mixed iodoacetates separated the two isomers, but these compounds are very unstable in the solid state and evolve iodine. They are, however, quite stable in chloroform solution, remaining unchanged after a week or two, provided they are kept below 0°C in the dark.

Physical Properties:

(i) **Iodolactone** (23), m.p. 157°C (lit.,[7] 157-157.5°C); ν_{max}(CHCl$_3$) 1780cm^{-1}; δ_H(CDCl$_3$) 2.20(m,2H, H$_2$-5), 2.80(dt, 1H,*J*=3.8Hz, *J*=2.5Hz, *J*=2.5Hz, H-6), 3.88(s,1H,H-3), 4.80(m,1H,H-4), 5.1(d,1H, *J*=2.5Hz. H-2), 5.4("t", 1H, *J*=2.5Hz, H-1, couples equally to H-2 and H-6); δ_C(CD$_3$)$_2$CO 36.4(t,C-5), 38.7(d,C-3 or C-6), 82.8, 85.3, 88.4(3xd, C-1, C-2, C-4), 146.6(s,*C*=O), one signal for either C-3 or C-6 was not detected; *m/z* (EI) 266(M$^+$, 70%), 139(M-I, 100%), 111(56%) [Found: C, 31.8; H, 2.8 Calculated for C$_7$H$_7$O$_3$I: C, 31.6; H, 2.7%]

(ii) **2α-Acetoxy-3β-iodo-6β-methoxycarbonyl-7-oxabicyclo[2.2.1]heptane (21)** ν_{max}(CHCl$_3$) 1800, 1740cm^{-1}; δ_H(CDCl$_3$) 1.85(m,1H,*J*$_{gem}$=13Hz, *J*$_{5\beta-6}$=4.4Hz, H-5β), 2.19(s,3H,COC*H*$_3$), 2.60(dd,1H,*J*$_{gem}$=13Hz, *J*$_{5\alpha,6}$= 4.4Hz, also find coupling with H-4, H-5α), 2.70(m,1H,H-3), 3.01(m,1H,H-6 , 3.72(s,3H,CO$_2$C*H*$_3$), 4.01(singlet with very fine coupling, 1H,H-4), 4.59(d,1H,*J*$_{1,2}$=2Hz,H-1), 6.46(t,1H,*J*$_{2,1}$=2Hz), also fine coupling of <<2Hz, H-2).

Nuclear Overhauser enhancements for the exo-iodoacetate (21) (spectrum recorded in CDCl$_3$)

Signal irradiated (Chemical Shift δ)	Observed nuclear overhauser enhancement
H-5α (2.60)	H-5α(5%), H-6(4%)
H-3 (2.70)	H-5α(7%), H-4(4%), H-2(8%)
H-6 (3.01)	H-5β(5%), H-3(3%), H-4(5%), H-1(6%)
H-4 (4.00)	H-5β(3%), H-3(3%), H-6(4%), H-1(2%)
H-1 (4.60)	H-4 (5%), H-6(3%)
H-2 (6.45)	H-3 (7%)

δ_C(CDCl$_3$) 21.0(q,CO*C*H$_3$), 22.2(t,C-5), 25.8(d,C-3), 45.3(d,C-6), 47.3(d,C-2), 52.1(q,CO$_2$*C*H$_3$), 84.9, 99.6(2xd, C-1, C-4), 170.0(s,*C*=O). Signal for *C*O$_2$CH$_3$ was not detected.

(iii) *3α-Acetoxy-2β-iodo-6β-methoxycarbonyl-7-oxabicyclo[2.2.1]heptane (22)* $\nu_{max}(CHCl_3)$ 1800, 1740cm^{-1}; $\delta_H(CDCl_3)$ 1.84-2.00(m,2H,H-5α, H-5β), 2.04(s,3H,$COC\underline{H}_3$), 2.64-3.02 (m,2H,H-6,H-2), 3.70(s,3H,$CO_2C\underline{H}_3$), 3.80(singlet with fine coupling, 1H,H-4), 4.63(d,1H,*J*=2Hz,H-1), 5.82(s,1H,H-3); $\delta_C(CDCl_3)$ 18.4(d,C-2), 21.2(d,$CO\underline{C}H_3$), 26.7(t,C-5), 45.1(d,C-6), 48.0(d,C-3), 52.3(q,$CO_2\underline{C}H_3$), 87.6, 98.9(2xd, C-1, C-4), 170.5(s,$\underline{C}$=O). Signal for $\underline{C}O_2CH_3$ was not detected; *m/z* (EI) for *both isomers* 340(M^+, 0.9%), 297(6%), 280(11%), 171(5%), 153(27%), 43(100%).

(b) *"Wet conditions"* A mixture of silver acetate (2.5g, 15mmol) and iodine (1.9g, 7.5mmol) in glacial acetic acid (35cm^3) was stirred at ambient temperature until all the iodine was consumed. At this point the adducts (1) (1.2g, 7.8mmol) in glacial acetic acid (10cm^3) were added. The mixture was heated at 50°C for further 20 minutes before glacial acetic acid (5cm^3) containing distilled water (0.14cm^3, 7.8mmol) was added. The reaction temperature was raised to 100°C and the reaction mixture left stirring for 5 hours. The yellow precipitate (AgI) was then filtered off and washed with chloroform (5cm^3). Evaporation of the filtrate under reduced pressure gave a colourless residue which was dissolved in chloroform, dried ($MgSO_4$) and evaporated. The t.l.c. analysis (SiO_2, 15% ethyl acetate in 60-80°C petrol) of this material showed three components (R_f 0.40, 0.34 and 0.33). The first component, which was also the major product, was separated on the Chromatotron from the two less polar components using the same conditions as those used in the previous experiment. It proved to be iodolactone (23) (1.20g, 60%) while the minor products (0.51g, 20%) were the mixed iodoacetonates (21) and (22) (ratio 1:1). A prolonged reaction time made little difference to the product composition, but an increase in temperature brought about destruction of the iodoacetates.

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