notes on methodology

A facile one-step synthesis of $\Delta^{1,4}$-3-keto bile acid esters by iodoxybenzene and benzeneselenic anhydride

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Abstract A facile one-step conversion of stereoisomeric methyl 3-hydroxycholanoates to 1,4-dien-3-one, by treatment in boiling toluene with iodoxybenzene catalyzed by benzeneselenic anhydride, is described. The direct oxidation-dehydrogenation at C-3 is applicable to other cholanoates (hyodeoxycholic, chenodeoxycholic, ursodeoxycholic, deoxycholic, and cholic) when the hydroxyl groups at C-6, C-7, or C-12 are protected. Without protection at C-6 and C-7, the products from hyodeoxycholic, chenodeoxycholic, ursodeoxycholic, and cholic esters are complex mixtures, whereas, methyl deoxycholate yields the 1,4-dien-3,12-dione cleanly.—**Iida, T., T. Shinohara, J. Goto, T. Nambara, and F. C. Chang.** A facile one-step synthesis of $\Delta^{1,4}$-3-keto bile acid esters by iodoxybenzene and benzeneselenic anhydride. *J. Lipid Res.* 1988. **29:** 1097–1101.

Supplementary key words oxidation-dehydrogenation reaction • conjugated dienones • 3-hydroxylated steroids • cholanoic acid derivatives

The biological importance of steroidal 1,4-dien-3-ones has generated much interest in their synthesis over the years. All the practical syntheses start from 3-hydroxy derivatives, and involve stepwise oxidation and subsequent dehydrogenation (or dehydrohalogenation) of an intermediate 3-ketone (or α-haloketone) (1). The available dehydrogenation reactions were rather unsatisfactory, and the multistep procedures generally led to poor yields, particularly for polysubstituted 3-hydroxy steroids.

Barton and coworkers (2–5) have introduced a reagent, consisting of iodoxybenzene with a catalytic amount of benzeneselenic anhydride (BSA),[2] which will convert certain 3-hydroxylated steroids by a one-step oxidation–dehydrogenation reaction smoothly into 1,4-dien-3-ones. In bile acids, they have demonstrated that methyl lithocholate and methyl deoxycholate are converted easily to the corresponding dienone and 1,4,9(11)-triene-3,12-dione, respectively (2). The results prompted us to apply the Barton reaction to other bile acids differing in the number, position, and configuration of hydroxyl groups and in the stereochemistry of A/B ring junction. This report is presented as an exploration of the usefulness and limitations of the reaction, specifically on cholanoic acids derivatives. Several cholestane compounds have been included in the study.

MATERIALS AND METHODS

Melting points (mp) were determined on an electric micro hot stage and are uncorrected. IR spectra were obtained on a Hitachi 215 double-beam spectrophotometer in $CHCl_3$ solution. UV spectra were determined in ethanol solution using a Model UV-200 Shimadzu double-beam spectrophotometer. ^{1}H-NMR spectra were obtained on a JEOL FX-90Q (90 MHz) instrument with $CDCl_3$ containing 1% Me_4Si as the solvent; chemical shifts are expressed in δ ppm relative to Me_4Si. High resolution mass spectra were recorded on a JEOL DX-303 mass spectrometer at 70 eV. HPLC was carried out on a Waters Associates system (M-45 pump; U6K sample loop injector; R401 differential refractometer) using a Nova-Pak C_{18} reversed-phase column (15 cm × 3.9 mm i.d., 5 μm) with methanol–water mixture as the mobile phase. TLC was performed on precoated silica gel 60 (0.25-mm layer thickness; E. Merck, Darmstadt, West Germany) using hexane–ethyl acetate or hexane–ethyl acetate–acetic acid mixture as the developing solvent.

The starting compounds (see **Scheme 1**) used in this study were methyl lithocholate (3α-OH-5β;1), methyl hyodeoxycholate (3α,6α-$(OH)_2$-5β;5), methyl chenodeoxycholate (3α,7α-$(OH)_2$-5β;7), methyl ursodeoxycholate (3α,7β-$(OH)_2$-5β;9), methyl deoxycholate (3α,12α-$(OH)_2$-5β;11), and methyl cholate (3α,7α,12α-$(OH)_3$-5β;14). They were obtained from the corresponding acids by the usual manner. The stereoisomers (2–4) of 1 were from collections in our laboratory. Methyl 3α-hydroxy-7α-acetoxy-5β-cholanoate (8),methyl 3α-hydroxy-12α-acetoxy-5β-cholanoate (12),methyl 3α-acetoxy-12α-hydroxy-5β-cholanoate (13), methyl 3α-hydroxy-7α,12α-diacetoxy-5β-cholanoate(15), methyl 3α,12α-dihydroxy-7α-acetoxy-5β-cholanoate(16), and methyl 3α,7α-diacetoxy-12α-hydroxy-5β-cholanoate(17) were prepared from 7,11, or 14. Methyl 3-oxo-6α-acetoxy-5β-cholanoate(6) and methyl-3-oxo-7β-acetoxy-5β-cholanoate(10) were prepared by silver carbonate–Celite oxidation (6), followed by acetylation of 5 and 9, respectively. Cholesterol (cholest-5-en-3β-ol;20) is available from com-

Abbreviations: IR, infrared; UV, ultraviolet; NMR, nuclear magnetic resonance; MS, mass spectrum; HPLC, high performance liquid chromatography; TLC, thin-layer chromatography; BSA, benzeneselenic anhydride.

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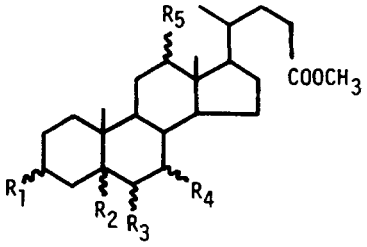
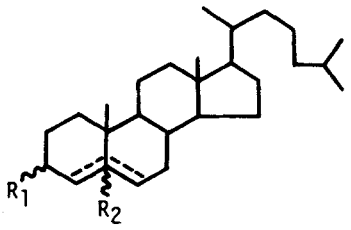
[2]Barton et al. (2) have also shown that meta-iodoxybenzoic acid-diphenyl diselenide is an alternative reagent with similar properties.





	R_1	R_2	R_3	R_4	R_5
1	α-OH	β-H	H	H	H
2	β-OH	β-H	H	H	H
3	α-OH	α-H	H	H	H
4	β-OH	α-H	H	H	H
5	α-OH	β-H	α-OH	H	H
6	=O	β-H	α-$OCOCH_3$	H	H
7	α-OH	β-H	H	α-OH	H
8	α-OH	β-H	H	α-$OCOCH_3$	H
9	α-OH	β-H	H	β-OH	H
10	=O	β-H	H	β-$OCOCH_3$	H
11	α-OH	β-H	H	H	α-OH
12	α-OH	β-H	H	H	α-$OCOCH_3$
13	α-$OCOCH_3$	β-H	H	H	α-OH
14	α-OH	β-H	H	α-OH	α-OH
15	α-OH	β-H	H	α-$OCOCH_3$	α-$OCOCH_3$
16	α-OH	β-H	H	α-$OCOCH_3$	α-OH
17	α-$OCOCH_3$	β-H	H	α-$OCOCH_3$	α-OH

	R_1	R_2
18	α-OH	α-H
19	β-OH	Δ^4
20	β-OH	Δ^5

Scheme 1.

mercial sources. 5α-Cholestan-3α-ol (18) and cholest-4-en-3β-ol (19) were from collections in our laboratory.

BSA was obtained from Aldrich (Milwaukee, WI). Iodoxybenzene was prepared from iodobenzene by the procedure described by Barton et al. (2).

General oxidation–dehydrogenation procedure

To a suspension of freshly prepared iodoxybenzene (1.6 g; 6.78 mmol) and BSA (0.16 g; 0.44 mmol) in toluene (20 ml) was added a solution of steroidal alcohol (2.05 mmol) in toluene (10 ml). The mixture was vigorously stirred under refluxing for 3 hr. The homogeneous solution was cooled at room temperature, and the organic layer was washed with water, dried over Drierite, and evaporated to dryness to give a light yellow oil. Chromatography of the oil over a column of silica gel (30:1 ratio) eluting with benzene–ethyl acetate (8:2 (v/v) for 21; 7:3 (v/v) for 22, 23, 24, 25, 26, and 31; 6:4 (v/v) for 27, 28, and 29; and 1:1 (v/v) for 30) afforded the purified product which was crystallized in an appropriate solvent.

Methyl 3-oxo-1,4-choladienoate (21)

Obtained from 1, 2, 3 and 4 in 80, 77, 70, and 72% yields, respectively; mp, 131–133°C (aq. methanol) (lit. mp, 131–133°C (2)). IR ν_{max} cm^{-1}: 1734 (C = O), 1600, 1625, 1665 ($\Delta^{1,4}$-3-oxo). UV λ_{max} nm (ε): 244.0 (11700). ^{1}H-NMR δ: 0.74 (3H, s, 18-Me), 0.91 (3H, d, J = 6.3 Hz, 21-Me), 1.22 (3H, s, 19-Me), 3.65 (3H, s, COOMe), 6.07

(1H, s, 4-H), 6.22 (1H, dd, $J_{1,2}$ = 9.9 Hz, $J_{2,4}$ = 1.8 Hz, 2-H), 7.05 (1H, d, J = 9.9 Hz, 1-H).

Methyl 3-oxo-6α-acetoxy-1,4-choladienoate (22)

Obtained from 6 in 73% yield; oil; IR ν_{max} cm^{-1}: 1740 (C = O), 1608, 1627, 1670 ($\Delta^{1,4}$-3-oxo), 1050, 1175, 1250 (acetate). UV λ_{max} nm (ε): 244.4 (15000). ^{1}H-NMR δ: 0.74 (3H, s, 18-Me), 0.92 (3H, d, J = 5.4 Hz, 21-Me), 1.28 (3H, s, 19-Me), 2.15 (3H, s, 6α-OCOMe), 3.66 (3H, s, COOMe), 5.55 (1H, brm, 6β-H), 6.25 (1H, s, 4-H), 6.25 (1H, dd, $J_{1,2}$ = 10.8 Hz, $J_{2,4}$ = 1.8 Hz, 2-H) 7.03 (1H, d, J = 10.8 Hz, 1-H). MS m/z (relative intensity): 442.2726(M^+, 2%, $C_{27}H_{38}O_5$ requires M, 442.2719), 382.2499($C_{25}H_{34}O_3$, 100%).

Methyl 3-oxo-7α-acetoxy-1,4-choladienoate (23)

Obtained from 8 in 77% yield; mp, 171-172°C (aq. methanol). IR ν_{max} cm^{-1}: 1740 (C = O), 1602, 1625, 1660 ($\Delta^{1,4}$-3-oxo), 1022, 1162, 1232 (acetate). UV λ_{max} nm (ε): 244.2 (15800). ^{1}H-NMR δ: 0.74 (3H, s, 18-Me), 0.92 (3H, d, J = 5.4 Hz, 21-Me), 1.25 (3H, s, 19-Me), 2.00 (3H, s, 7α-OCOMe), 3.66 (3H, s, COOMe), 5.05 (1H, m, 7β-H), 6.01 (1H, s, 4-H), 6.26 (1H, dd, $J_{1,2}$ = 9.9 Hz, $J_{2,4}$ = 1.8 Hz, 2-H), 7.07 (1H, d, J = 9.9 Hz, 1-H). Anal. calcd. for $C_{27}H_{38}O_5$: C, 73.27; H, 8.65. Found: C, 73.42; H, 8.81.

Methyl 3-oxo-7β-acetoxy-1,4-choladienoate (24)

Obtained from 10 in 68% yield; mp, 140-141°C (aq. methanol). IR ν_{max} cm^{-1}: 1722 (C = O), 1601, 1626, 1660 ($\Delta^{1,4}$-3-oxo), 1022, 1164, 1242 (acetate). UV λ_{max} nm (ε): 243.6 (14300). ^{1}H-NMR δ: 0.76 (3H, s, 18-Me), 0.92 (3H, d, J = 5.4 Hz, 21-Me), 1.28 (3H, s, 19-Me), 2.04 (3H, s, 7β-OCOMe), 3.66 (3H, s, COOMe), 4.59 (1H, brm, 7α-H), 6.12 (1H, s, 4-H), 6.24 (1H, dd, $J_{1,2}$ = 10.8 Hz, $J_{2,4}$ = 1.8 Hz, 2-H), 7.04 (1H, d, J = 9.9 Hz, 1-H). Anal. calcd. for $C_{27}H_{38}O_5$: C, 73.27; H, 8.65. Found: C, 73.14; H, 8.74.

Methyl 3,12-dioxo-1,4-choladienoate (25)

Obtained from 11 in 72% yield; oil; IR ν_{max} cm^{-1}: 1704, 1735 (C = O), 1600, 1622, 1660 ($\Delta^{1,4}$-3-oxo). UV λ_{max} nm (ε): 244.0 (10400). ^{1}H-NMR δ: 0.86 (3H, d, J = 5.4 Hz, 21-Me), 1.11 (3H, s, 18-Me), 1.31 (3H, s, 19-Me), 3.66 (3H, s, COOMe), 6.10 (1H, s, 4-H), 6.25 (1H, dd, $J_{1,2}$ = 9.9 Hz, $J_{2,4}$ = 1.8 Hz, 2-H), 6.87 (1H, d, J = 9.9 Hz, 1-H). MS m/z (relative intensity): 398.2437 (M^+, 78%, $C_{25}H_{34}O_4$ requires M, 398.2457).

Methyl 3-oxo-12α-acetoxy-1,4-choladienoate (26)

Obtained from 12 in 78% yield; oil; IR ν_{max} cm^{-1}: 1735 (C = O), 1602, 1625, 1660 ($\Delta^{1,4}$-3-oxo), 1022, 1174, 1242 (acetate). UV λ_{max} nm (ε): 246.6 (12900). ^{1}H-NMR δ: 0.81 (3H, s, 18-Me), 0.81 (3H, d, J = 5.4 Hz, 21-Me), 1.21 (3H, s, 19-Me), 2.03 (3H, s, 12α-OCOMe), 3.66 (3H, s, COOMe), 5.11 (1H, m, 12β-H), 6.09 (1H, s, 4-H), 6.21 (1H, dd, $J_{1,2}$ = 10.8 Hz, $J_{2,4}$ = 1.8 Hz, 2-H), 6.93 (1H, d, J = 10.8 Hz, 1-H). MS m/z (relative intensity): 442.2687 (M^+, 5%, $C_{27}H_{38}O_5$ requires M, 442.2719), 382.2500 ($C_{25}H_{34}O_3$, 90%).

Methyl 3-oxo-7α,12α-diacetoxy-1,4-choladienoate (27)

Obtained from 15 in 73% yield; mp, 171-172°C (acetone -hexane). IR ν_{max} cm^{-1}: 1735 (C = O), 1602, 1625, 1665 ($\Delta^{1,4}$-3-oxo), 1030, 1174, 1210, 1235 (acetate). UV λ_{max} nm (ε): 246.8 (12600). ^{1}H-NMR δ: 0.81 (3H, s, 18-Me), 0.81 (3H, d, J = 5.4 Hz, 21-Me), 1.23 (3H, s, 19-Me), 2.04 and 2.07 (each 3H, s, 7α- and 12α-OCOMe), 3.66 (3H, s, COOMe), 5.09 (2H, m, 7β- and 12β-H), 6.03 (1H, s, 4-H), 6.25 (1H, dd, $J_{1,2}$ = 9.9 Hz, $J_{2,4}$ = 1.8 Hz, 2-H), 6.95 (1H, d, J = 9.9 Hz, 1-H). Anal. calcd. for $C_{29}H_{40}O_7$: C, 69.57; H, 8.05. Found: C, 69.62; H, 8.04.

Methyl 3,12-dioxo-7α-acetoxy-1,4-choladienoate (28)

Obtained from 16 in 76% yield; mp, 245-246°C (acetone-hexane). IR ν_{max} cm^{-1}: 1700, 1725 (C = O), 1600, 1620, 1660 ($\Delta^{1,4}$-3-oxo), 1018, 1168, 1230 (acetate). UV λ_{max} nm (ε): 238.2 (21900). ^{1}H-NMR δ: 0.87 (3H, d, J = 5.4 Hz, 21-Me), 1.12 (3H, s, 7α-OCOMe), 3.66 (3H, s, COOMe), 5.12 (1H, m, 7β-H), 6.05 (1H, s, 4-H), 6.29 (1H, dd, $J_{1,2}$ = 9.9 Hz, $J_{2,4}$ = 1.8 Hz, 2-H), 6.90 (1H, d, J = 9.9 Hz, 1-H). Anal. calcd. for $C_{27}H_{36}O_6$: C, 71.02; H, 7.95. Found: C, 70.68; H, 7.74.

Methyl 3α-acetoxy-12-oxo-5β-cholanoate (29)

Obtained from 13 in 87% yield; mp, 152-153°C (aq. methanol) (lit. mp, 145-147°C and 153.5-154.5°C (7)). IR ν_{max} cm^{-1}: 1700, 1735 (C = O), 1030, 1208, 1242 (acetate). ^{1}H-NMR δ: 0.86 (3H, d, J = 6.3 Hz, 21-Me), 1.02 (6H, s, 18- and 19-Me), 2.01 (3H, s, 3α-OCOMe), 3.66 (3H, s, COOMe), 4.69 (1H, brm, 3β-H).

Methyl 3α,7α-diacetoxy-12-oxo-5β-cholanoate (30)

Obtained from 17 in 81% yield; mp, 176-178°C (aq. methanol) (lit. mp, 177-178.5°C and 179-181°C (7)). IR ν_{max} cm^{-1}: 1700, 1730 (C = O), 1022, 1060, 1170, 1245 (acetate). ^{1}H-NMR δ: 0.86 (3H, d, J = 6.3 Hz, 21-Me), 1.04 (6H, s, 18- and 19-Me), 2.02 and 2.03 (each 3H, s, 3α- and 7α-OCOMe), 3.66 (3H, s, COOMe), 4.58 (1H, brm, 3β-H), 4.99 (1H, m, 7β-H).

Cholesta-1,4-dien-3-one (31)

Obtained from 18 and 19 in 76% and 63% yields, respectively; mp, 113-114°C (methanol) (lit. mp, 110-112°C (8)). IR ν_{max} cm^{-1}: 1598, 1610, 1650 ($\Delta^{1,4}$-3-oxo). UV λ_{max} nm (ε): 244.0 (16800). ^{1}H-NMR δ: 0.74 (3H, s, 18-Me), 0.86 (6H, d, J = 5.4 Hz, 26- and 27-Me), 0.90 (3H, d, J = 5.4 Hz, 21-Me), 1.23 (3H, s, 19-Me), 6.07 (1H, s, 4-H), 6.22 (1H, dd, $J_{1,2}$ = 10.8 Hz, $J_{2,4}$ = 1.8 Hz, 2-H), 7.06 (1H, d, J = 9.9 Hz, 1-H).

RESULTS AND DISCUSSION

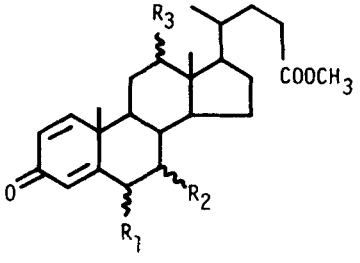
The oxidation–dehydrogenation reaction was carried out by a slight modification of Barton's iodoxybenzene–BSA–toluene method (2). When 3-hydroxylated compounds in boiling toluene are treated with iodoxybenzene (3.3 mmol-equivalents) alone, only C-3 oxidized products were recovered. However, by adding a catalytic amount of BSA (0.2 mmol-equivalents), both oxidation and dehydrogenation reactions proceeded smoothly without need to isolate the intermediate 3-ketones, and afforded the conjugated $\Delta^{1,4}$-3-keto derivatives (see **Scheme 2**) as described below. The oxidation–dehydrogenation products were easily isolated by a short chromatography on silica gel eluting with benzene–ethyl acetate mixtures. The yields were between 64 and 80%.

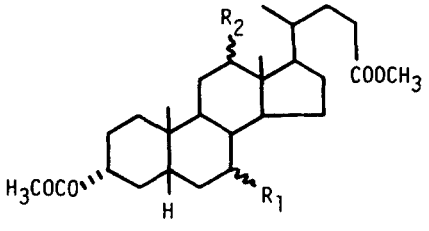
As contrasted with the clean reactions reported (2) for methyl lithocholate (1) and methyl deoxycholate (11), when methyl cholate (14) was subjected to the iodoxybenzene–BSA reaction , a complex mixture of products was obtained, which led to the conjecture that the free 7α-hydroxyl group might be responsible. This was confirmed when methyl chenodeoxycholate (7) in the reaction was found to also give a complex mixture while its 7-acetate derivative (8) cleanly yielded the 7α-acetoxy-1,4-dienone 23.

The successful reaction on the methyl cholate acetate derivatives, the 7,12-diacetate 15 and 7-monoacetate 16, reveals two further findings. First, protection of the 12α-hydroxyl also is effective in obtaining a clean reaction: 3α-OH-7α,12α-$(OAc)_2$ 15 gave 7α,12α-diacetoxy-1,4-dienone 27. Second, an hydroxyl group at C-12 does not interfere with the overall reaction, but is oxidized without simultaneous dehydrogenation at C-9, to yield the 7α-acetoxy-1,4-dien-3,12-dione 28 from 16. The latter result appears to conflict with that reported by Barton et al. (2), who obtained the 1,4,9(11)-trien-3,12-dione in the reaction with 11, but the contradiction can be explained by comparison of the differing reaction conditions. Their reaction with 11 was performed with a different reagent, meta-iodoxybenzoic acid–diphenyl diselenide, at a higher molar equivalent and the reaction took place for a much longer period of time (71 vs. 3 hr), which apparently allows dehydrogenation at C-9 to take place.

Consistent with the above findings, methyl deoxycholate 12-acetate (12) yields the oxidation–dehydrogenation product, 1,4-dien-3-one-12α-acetate 26, whereas methyl deoxycholate 3-acetate (13) and methyl cholate 3,7-diacetate (17) afford only C-12 oxidized products, 29 and 30.

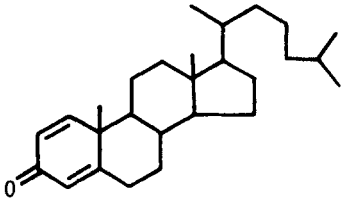
Both methyl hyodeoxycholate (5) and methyl ursodeoxycholate (9) fail to give clean products in the iodoxybenzene–BSA reaction, presumably because their respective 6α- and 7β-hydroxyl groups are unprotected. Since they are the only compounds with these hydroxyl configurations included in this work, it would be desirable to treat their protected





	R_1	R_2	R_3
21	H	H	H
22	α-OCOCH₃	H	H
23	H	α-OCOCH₃	H
24	H	β-OCOCH₃	H
25	H	H	=O
26	H	H	α-OCOCH₃
27	H	α-OCOCH₃	α-OCOCH₃
28	H	α-OCOCH₃	=O

	R_1	R_2
29	H	=O
30	α-OCOCH₃	=O



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Scheme 2.

derivatives similarly to test the conjecture. However, as neither compound 5 nor 9 is readily available as derivatives protected in the respective 6 and 7 positions, we have substituted for them the 3-oxo-6α-acetoxy (6) and 3-oxo-7β-acetoxy (10) compounds, and find that the reactions proceed smoothly to yield respectively, 6α-acetoxy-1,4-dien-3-one (22) and 7β-acetoxy-1,4-dien-3-one (24), as hoped for.

If a transient 3-oxo intermediate is indeed involved in the oxidation–dehydrogenation process, either hydroxyl epimer at C-3 would be expected to undergo the reaction to yield the same product, but a further question remains to be answered: what would be the effect of a change in A/B ring junction? Both these points were cleared up when identical experiments with the four 3-hydroxy-5-H stereoisomers, 1 to 4, all afforded the same dienone 21 in good yield; thus, the oxidation–dehydrogenation reaction proceeds well regardless of the configuration of the 3-hydroxyl or the ring geometry at C-5. The epimeric 5α-cholestan-3ζ-ols had both been reported previously (4) to give the identical dienone 31. We have confirmed that 5α-cholestan-3α-ol (18) gives dienone 31, and have found that while the allylic alcohol, cholest-4-en-3β-ol (19) also gives dienone 31, the homoallylic compound, cholesterol (20), under identical conditions results in a complex mixture.

The use of diphenyl diselenide (2, 4) as catalyst, instead of BSA, provided essentially identical results mentioned above, according to TLC and HPLC analyses. Thus, the iodoxybenzene–BSA (or diphenyl diselenide) reaction of 3-hydroxylated bile acid methyl esters is highly regioselective and offers an attractive one-step route to the $\Delta^{1,4}$-3-ketones.

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