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A Remarkable Multiple Rearrangement Process in the Bromination of *endo*-3-Bromo-4-Methylcamphor: Intermediates for Triterpenoid Synthesis

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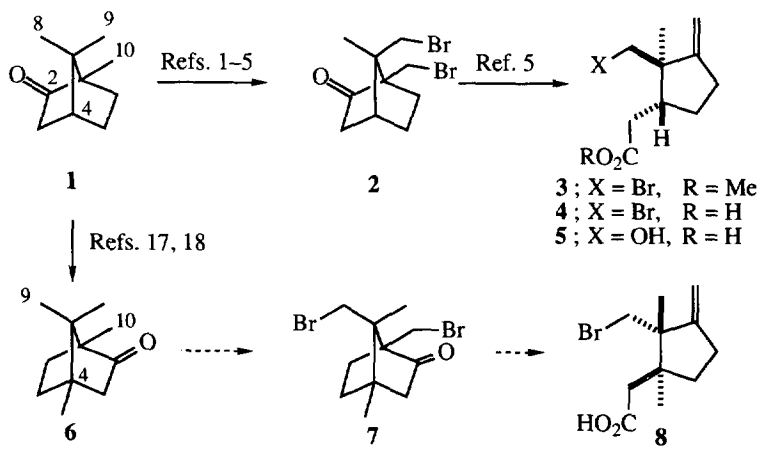
Abstract: The remarkable transformation of *endo*-3-bromo-4-methylcamphor (**9**) to *endo*-3,9-dibromo-4-(bromomethyl)camphor (**11**) forms the basis of a new approach to intermediates for the synthesis of lanostane triterpenoids, euphane triterpenoids and 14α-methyl steroids.

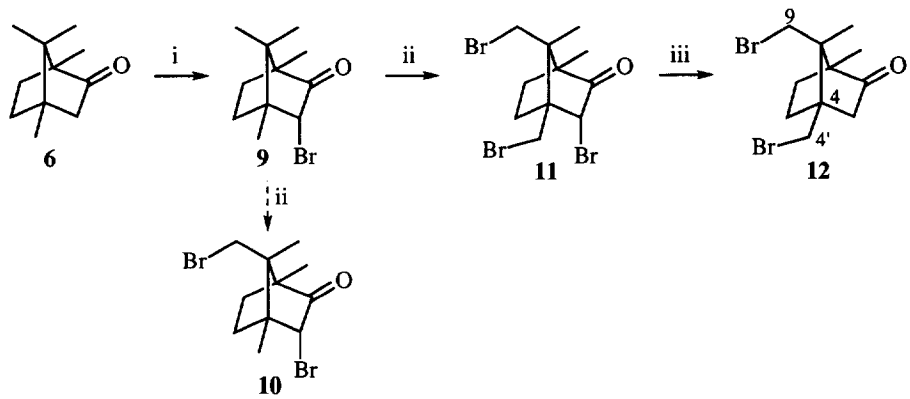
In previous reports we described the conversion of (+)-camphor (**1**) to (+)-9,10-dibromocamphor (**2**)[1-6] [Scheme 1] and its subsequent conversion, in high yield, to bromoester **3**,[5] bromoacid **4**,[5] and hydroxyacid **5**.[5] These cyclopentanoid compounds and their respective enantiomers, derived from (–)-camphor (***ent*-1**), are now recognized as versatile intermediates in terpenoid[7-12] and steroid[13-16] synthesis. An analogous series of reactions (Scheme 1) using (–)-4-methylcamphor (**6**)[17,18] or its enantiomer ***ent*-6** as starting material and 9,10-dibromo-4-methylcamphor (**7**) as intermediate would be expected to provide bromoacid **8** or its enantiomer ***ent*-8** and these compounds could have potential as enantiopure intermediates for the synthesis of lanostane-type and euphane-type triterpenoids respectively[19]. It seemed reasonable to assume that 9,10-dibromo-4-methylcamphor



Scheme 1

(**7**) could be synthesized from (–)-4-methylcamphor (**6**) by the reaction sequence previously used[1,5] to convert (+)-camphor (**1**) to (+)-9,10-dibromocamphor (**2**). As described previously[1,5,15], this sequence involves C(3)-bromination, C(9)-bromination, C(10)-bromination and, finally, chemospecific debromination of the C(3)-bromo substituent.

Thus, by analogy, 4-methylcamphor (**6**)* [derived from (+)-camphor (**1**)][17,18] was converted to *endo*-3-bromo-4-methylcamphor (**9**) (Scheme 2) and then subjected to the usual C(9)-bromination conditions [Br_2,



(i) Br_2, HOAc, 80 °C, 24 h [96%] (ii) Br_2, $ClSO_3H$, 19 h [84%] (iii) Zn, HOAc : Et_2O (1:1) 0 °C [81%].

Scheme 2

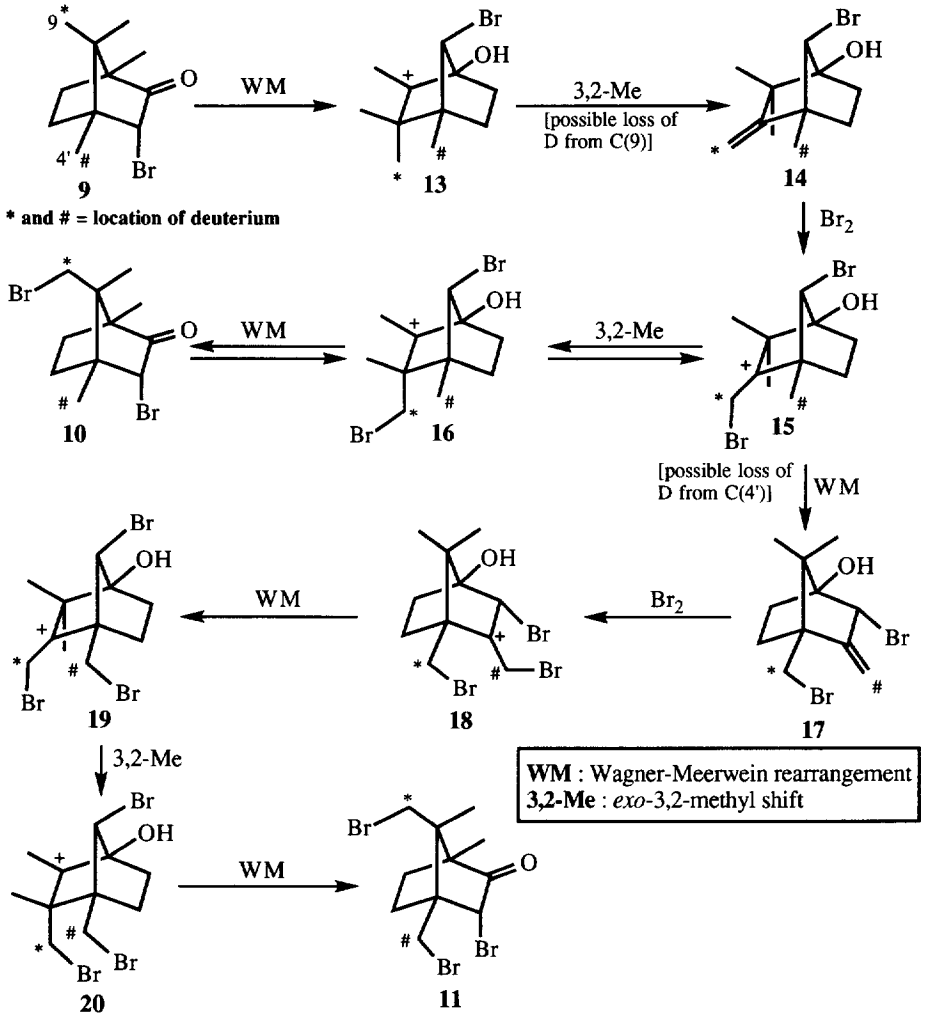
$ClSO_3H$, 24 h] with the expectation that this would provide *endo*-3,9-dibromo-4-methylcamphor (**10**). We were surprised to find, however, that the nmr of the major product in this reaction indicated the presence of two bromomethyl [CH_2Br] groups. That the "extra" bromine atom was not associated with the C(10) methyl group was deduced from the failure of this product to undergo ring cleavage reactions typical[5,25,26] of 10-bromocamphor derivatives. Nmr evidence and mechanistic considerations led to the conclusion[27] that this product was *endo*-3,9-dibromo-4-(bromomethyl)camphor (**11**) and this was subsequently confirmed by X-ray crystallographic analysis[28]. Minor products in the reaction were identified as *endo*-3,9-dibromo-4-methylcamphor (**10**) and *endo*-3,9,9-tribromo-4-methylcamphor.

Attempts to find reaction conditions that promoted exclusive formation of *endo*-3,9-dibromo-4-methylcamphor (**10**) were unsuccessful. For example, when the reaction of *endo*-3-bromo-4-methylcamphor (**9**) with bromine (2.2 eq.) in chlorosulfonic acid was stopped after 5 min, GLC analysis showed that the product mixture (~1:1) consisted of starting material **9** and *endo*-3,9-dibromo-4-(bromomethyl)camphor (**11**). Only a small amount [<5%] of *endo*-3,9-dibromo-4-methylcamphor (**10**) was detected. However, when *endo*-3-bromo-4-methylcamphor (**9**) was allowed to react with one equivalent of bromine in chlorosulfonic acid, the

* Modifications and corrections to the previously published procedures[17] for the synthesis of enantioenriched (–)-4-methylcamphor (**6**) [*e.e.* 60%] from (+)-camphor (**1**) and its subsequent conversion to *endo*-3,9-dibromo-4-(bromomethyl)camphor (**11**) as well as revised nmr assignments are provided in the experimental section. The synthesis of enantiopure (–)-4-methylcamphor (**6**) has recently been described[18]. However, since one of the steps in the latter synthetic route remains to be optimized, enantioenriched rather than enantiopure material was used in this investigation.

reaction product was a mixture [~1:1] of *endo*-3,9-dibromo-4-methylcamphor (**10**) and *endo*-3,9-dibromo-4-(bromomethyl)camphor (**11**) (combined yield ~61%). These two bromocamphor derivatives could be separated easily and when pure *endo*-3,9-dibromo-4-methylcamphor (**10**) was treated with one equivalent of bromine in chlorosulfonic acid, the only major product was *endo*-3,9-dibromo-4-(bromomethyl)camphor (**11**)

A plausible mechanism for the remarkable transformation of *endo*-3-bromo-4-methylcamphor (**9**) to *endo*-3,9-dibromo-4-(bromomethyl)camphor (**11**) is shown in Scheme 3 and involves a combination of four Wagner-Meerwein rearrangements, two *exo*-3,2-methyl shifts, and two bromination steps. The formation of



9 **13** **14**

* and # = location of deuterium

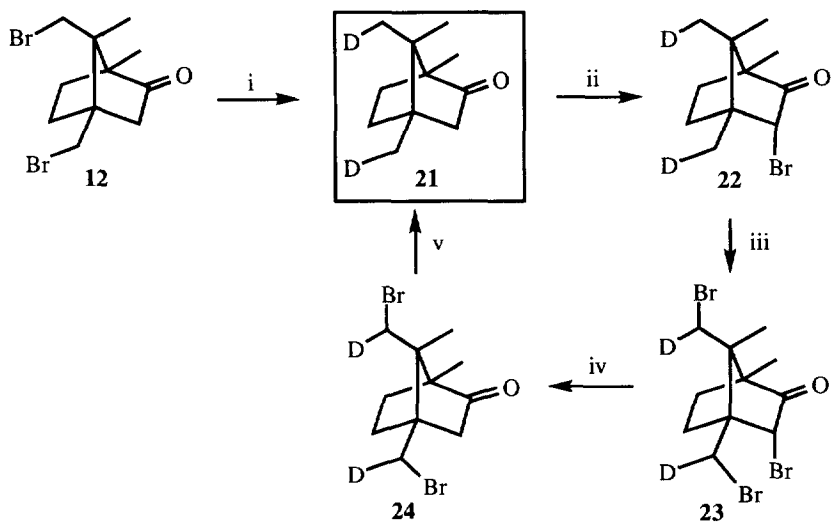
10 **16** **15** **17** **18** **19** **20** **11**

Scheme 3

endo-3,9-dibromo-4-methylcamphor (**10**) as a minor by-product can be explained by assuming that the intermediate carbocation **15** undergoes *exo*-3,2-methyl shift less rapidly than Wagner-Meerwein rearrangement.

Finally the formation of *endo*-3,9,9-tribromo-4-methylcamphor is analogous to the formation of (+)-*endo*-3,9,9-tribromocamphor from (+)-*endo*-3-bromocamphor[29–31]. If the sequence of reactions formulated in Scheme 3 does in fact represent the pathway taken during the dibromination reaction, then two predictions can be made. First of all, there should be no overall change in the relative position of any of the four methyl groups in *endo*-3-bromo-4-methylcamphor (**9**) during the dibromination process. Secondly, the proposed involvement of exocyclic intermediates **14** and **17**, derived from **13** and **15** respectively, should result in a loss of protons from the C(9) and C(4') methyl groups in **9** and accordingly, a similar, detectable loss of deuterons from the C(9) and C(4') methyl groups in the deuterated analogue **22**.

Experimental support for this mechanism was obtained by converting 9-bromo-4-(bromomethyl)camphor (**12**) to 9-deuterio-4-(deuteriomethyl)camphor (**21**) [Scheme 4] and subjecting this compound to the dibromination-debromination sequence to provide 9-bromo-9-deuterio-4-(bromodeuterio-



(i) Bu_3SnD, AIBN, benzene [58%] (ii) Br_2, HOAc, 80 °C, 24 h [96%] (iii) Br_2, $ClSO_3H$, 19 h [84%] (iv) Zn, HOAc : Et_2O (1:1), 0 °C [81%] (v) Bu_3SnH, AIBN, benzene [64%].

Scheme 4

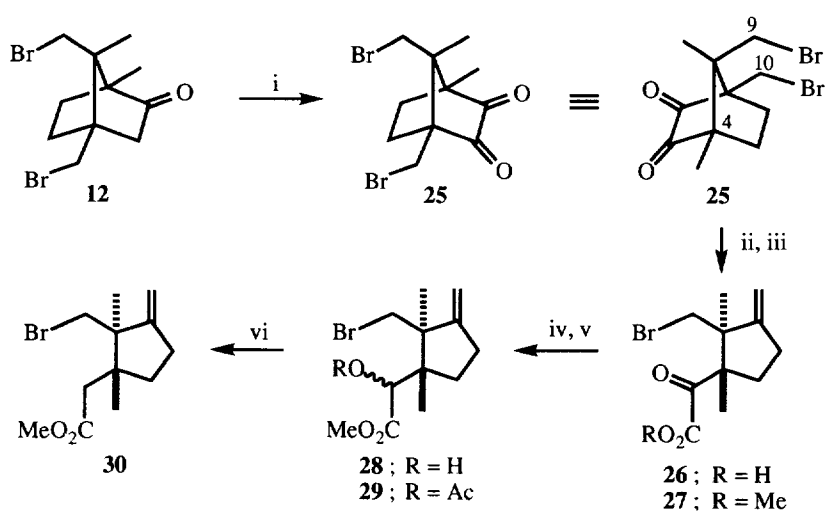
methyl)camphor (**24**). Subsequent reductive removal [Bu_3SnH, AIBN, C_6H_6] of the bromo substituents in **24** completed the cycle and *regenerated* 9-deuterio-4-(deuteriomethyl)camphor (**21**). The ^1H nmr spectrum [400 MHz] of the *initial* sample of **21** has singlets at 0.69 ppm [C(8) methyl] and 0.90 ppm [C(10)-methyl] as well as two apparent triplets at 0.80 ppm [C(9)-deuteriomethyl] and 1.00 ppm [C(4)-deuteriomethyl]. In addition to the evidence previously reported[17] to support these assignments, a correlation [^4J or W coupling] between the singlet at 0.69 ppm and the triplet at 0.80 ppm was recorded in the 400 MHz COSY spectrum. As expected the chemical shifts of the C(4') and C(9) protons [1.00 and 0.80 ppm] in the deuterated compound **21** are shifted upfield relative to the corresponding protons [1.02 and 0.81] in 4-methylcamphor (**6**). There are, however, two weak singlet methyl signals at the latter chemical shifts in the nmr spectrum of **21** and this indicates the presence of unlabelled 4-methylcamphor (**6**) as an impurity in this *initial* sample of **21**. It is believed that this inseparable

impurity originates from the residual Bu_3SnH (~3%) that is present in the commercially obtained Bu_3SnD reagent. Integration of the ^1H nmr spectrum indicated that the *initial* sample of 9-deuterio-4-(deuteriomethyl)camphor (**21**) contained (4 ± 2)% of 4-methylcamphor (**6**).

When the spectrum of *regenerated* 9-deuterio-4-(deuteriomethyl)camphor (**21**) was compared with the spectrum of the *initial* sample of **21**, it was noted that the only significant difference between them was the presence of relatively stronger signals at 0.81 [C(9)-methyl] and 1.02 ppm [C(4)-methyl], that is, a significant loss of deuterium from the C(9)-deuteriomethyl and C(4)-deuteriomethyl groups had occurred during the dibromination process. From the nmr spectra of *regenerated* 9-deuterio-4-(deuteriomethyl)camphor (**21**) the protio content [unlabelled 4-methylcamphor] was found to be (25 ± 7)%. Confirmation of this estimate was obtained by recording the integrals of the signals due to the C(9)-CH_2Br and C(9)-CHDBr groups in 9-bromo-9-deuterio-4-(bromodeuteriomethyl)camphor (**24**) and its synthetic precursor, *endo*-3,9-dibromo-9-deuterio-4-(bromodeuteriomethyl)camphor (**23**) [*cf.* Scheme 4].

The spectroscopic evidence outlined above is consistent with the reaction pathway shown in Scheme 2 and the significant loss of deuterium from the C(9) and C(4') positions during the dibromination reaction provides evidence to support the proposed involvement of *exo*-methylene intermediates **14** and **17**.

The versatility of 9,10-dibromocamphor (**2**)[1–6] as an intermediate in terpenoid[7–12] and steroid synthesis[13–16] is due to the fact that it undergoes efficient ring cleavage[5] to produce cyclopentanoid compounds



(i) SeO_2, Ac_2O [59%] (ii) KOH, MeOH [85%] (iii) K_2CO_3, DMF, MeI [82%] (iv) $NaBH_4$, MeOH [76%] (v) Ac_2O, C_5H_5N [63%] (vi) SmI_2, THF, HMPA, MeOH [41%].

Scheme 5

in high yield. Since this chemical reactivity is associated with the presence of an α,α-disubstituted β-bromocarbonyl (*e.g.* 10-bromocarbonyl) structural sub-unit, 9-bromo-4-(bromomethyl)camphor (**12**) does not undergo similar ring cleavage to produce terpenoid intermediates. Fortunately, however, this structural sub-unit can be created easily by transformation [SeO_2 (two-fold excess), Ac_2O] of **12** to 9,10-dibromo-4-

methylcamphorquinone (**25**; Scheme 5), a bright yellow, crystalline solid (UV-Vis: λ_{max} 478 nm; log ε = 1.63). Subsequent treatment of **25** with NaOH/MeOH at room temperature for ten minutes resulted in efficient cleavage of the C(1)–C(2) bond and provided the cyclopentanoid bromo-α-ketoacid (**26**) [Scheme 5] in ~85% yield. Esterification [K_2CO_3, DMF; MeI] followed by chemoselective reduction [$NaBH_4$, MeOH] and acetylation [Ac_2O, C_5H_5N] provided bromo α-acetoxyester (**29**) as a mixture [~2:1] of diastereomers. Finally reductive cleavage of the α-acetoxy group in **29** with SmI_2, THF, HMPA[32-34] in an O_2-free atmosphere provided bromoester (**30**) in ~40% yield.

Current studies are concerned with increasing the yield in the latter reaction and establishing the use of bromoester (**30**) in triterpenoid synthesis.

ACKNOWLEDGMENTS

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EXPERIMENTAL

General Experimental

Detailed general experimental procedures and techniques from our laboratory have been reported recently.[12] All solvents used for the preparation of SmI_2 were de-gassed by the freeze-pump-thaw method, and particular care was taken to exclude oxygen from the reaction flask while carrying out reactions involving SmI_2.[35] Ultraviolet-Visible spectra were recorded on a Hewlett-Packard HP-8452A diode array spectrophotometer.

(–)-4-Methylcamphor (6)

The following modification to the published procedure[17] was used. Jones reagent [prepared from chromium(VI) oxide (18.1 g, 0.181 mol), water (40 mL), and concentrated sulfuric acid (10 mL)] was added, dropwise over 20 min, to a solution of 4-methylisoborneol (30.4 g, 0.181 mol) in acetone (75 mL) at 0 °C. After 2 h at 0° the reaction mixture was worked up in the usual way to yield 4-methylcamphor (**6**) as a volatile, white solid (29.6 g, 99%) that could be used directly in the next reaction. IR and low- and high-resolution mass spectral data for **6** were in agreement with those reported previously.[17] **^{1}H nmr ($CDCl_3$, 400 MHz):** δ 2.06 (dd, J = 18.1, 3.0 Hz, 1H; H(3_{exo})), 1.85 (d, J = 18.1 Hz, 1H; H(3_{endo})), 1.57–1.73 (m, 2H), 1.33–1.42 (m, 2H), 1.02 (s, 3H; H(4')), 0.90 (s, 3H; H(10)), 0.80 (s, 3H; H(9)), 0.69 (s, 3H; H(8)). **^{13}C nmr ($CDCl_3$, 75 MHz):** δ 219.3 (C(2)), 59.7, 49.0, 48.1, 45.5, 34.3, 29.6, 17.5, 15.8, 15.5, 10.1.

endo-3-Bromo-4-methylcamphor (9)

The following modification to the published procedure[17] was used. To a solution of 4-methylcamphor (**6**; 27.6 g, 0.166 mmol) in glacial acetic acid (250 mL) at 80 °C was added, dropwise over 30 min, a solution

of bromine (9.4 mL, 29 g, 0.18 mmol) in glacial acetic acid (10 mL). The red-orange solution was stirred at 80 °C for 18 h, allowed to cool to room temperature, and poured cautiously into a saturated aq. $NaHSO_3$ solution (~100 mL). The aqueous solution was decanted and extracted with Et_2O (2 × 250 mL) while the precipitated crude product was dissolved in Et_2O (250 mL). The combined organic solutions were worked up in the usual way to provide a light orange-brown solid that was crystallized from methanol to yield *endo*-3-bromo-4-methylcamphor as white crystals (24.9 g, 61%). Subsequent purification of the mother liquor by flash column chromatography [10% Et_2O–pet. ether] yielded a minor by-product, 3,3-dibromo-4-methylcamphor (1.2 g) and upon further elution, *endo*-3-bromo-4-methylcamphor (**9**; 14.3 g, 35%; total yield 96%) as a volatile, white solid. ^1H nmr, IR, low- and high-resolution mass spectral data for **9** were in agreement with those reported previously.[17] **^{13}C nmr ($CDCl_3$, 75 MHz)**: δ 212.3 (C(2)), 60.4 (C(3)), 59.0, 50.8, 47.0, 30.1, 29.1, 17.4, 17.1, 13.8, 10.2.

endo-3,9-Dibromo-4-(bromomethyl)camphor (11)[17]

The following modification to the published procedure[17] was used. To a 250-mL, single-neck, round-bottom flask containing *endo*-3-bromo-4-methylcamphor (**9**; 24.9 g, 0.102 mmol) and immersed in an ice-water bath was added in rapid succession chlorosulfonic acid (20 mL) and bromine (12.0 mL, 37.3 g, 0.233 mmol). The solution was stirred at 0 °C for 10 min and then at room temperature for 18 h. The reaction mixture was poured cautiously onto ice (~200 mL) and saturated aq. $NaHSO_3$ (100 mL) was added slowly. The aqueous mixture was extracted with dichloromethane or chloroform (5 × 100 mL). The organic extracts were washed with water (5 × 500 mL), neutralized with saturated aq. $NaHCO_3$ (3 × 250 mL), washed with brine (3 × 250 mL), dried over anhydrous $MgSO_4$, and concentrated under reduced pressure to yield a yellow-brown solid that was crystallized from MeOH–$CHCl_3$[4:5]; 90 mL] to provide pure *endo*-3,9-dibromo-4-(bromomethyl)camphor (**11**; 22.4 g, 55%). The mother liquor was purified further, in two batches, by flash column chromatography (15% Et_2O–pet. ether) to yield the by-products, *endo*-3,9-dibromo-4-methylcamphor (**10**; 0.5897 g), *endo*-3,9,9-tribromo-4-(bromomethyl)camphor (0.5779 g), and upon further elution, the desired *endo*-3,9-dibromo-4-(bromomethyl)camphor (**11**; 12.0 g, 29%; total yield 84%) as a white solid; mp 142.0–143.0 °C (*lit.*[17] 142.5–143.5 °C). IR, low- and high-resolution mass spectral data for **11** are in agreement with those reported previously.[17] **^1H nmr ($CDCl_3$, 400 MHz):** δ 4.92 (d, J = 2.3 Hz, 1H; H(3_{exo})), 4.06 (d, J = 11.6 Hz, 1H; H($4'_A$)), 3.74 (d, J = 11.0 Hz, 1H; H(9_A)), 3.52 (d, J = 11.6 Hz, 1H; H($4'_B$)), 3.46 (d, J = 11.0 Hz, 1H; H(9_B)), 2.19 (ddd, J = 13.5, 9.7, 4.0 Hz, 1H; H(5_{endo})), 1.82 (dddd, J = 13.5, 13.5, 5.0, 2.3 Hz, 1H; H(5_{exo}), 1.70 (ddd, J = 13.5, 13.5, 3.9 Hz, 1H; H(6_{exo})), 1.52 (ddd, J = 13.5, 9.7, 5.0 Hz, 1H; H(6_{endo})), 1.24 (s, 3H; H(8)), 1.03 (s, 3H; H(10)). **^{13}C nmr ($CDCl_3$, 75 MHz):** δ 208.6 (C(2)), 61.1, 55.4, 54.2, 50.6, 35.8, 31.3, 29.6, 28.2, 16.7, 10.4.

9-Bromo-4-(bromomethyl)camphor (12)[17]

9-Bromo-4-(bromomethyl)camphor (**12**) was prepared according to the previously reported method.[17] ^1H nmr, IR, low- and high-resolution mass spectral data for **12** are in agreement with those reported previously.[17] **^{13}C nmr ($CDCl_3$, 75 MHz):** δ 213.4 (C(2)), 61.9, 52.0, 51.3, 47.7, 36.1, 35.8, 31.8, 28.4, 15.3, 10.6.

9-Deuterio-4-(deuteriomethyl)camphor (21)[17]

9-Deuterio-4-(deuteriomethyl)camphor (**21**) was prepared according to the previously reported method.[17] IR and low- and high-resolution mass spectral data are in agreement with those reported previously.[17] **^{1}H nmr (CDCl$_3$, 400 MHz):** δ 2.07 (dd, J = 18.2, 3.0 Hz, 1H; H(3_{exo})), 1.85 (d, J = 18.2 Hz, 1H; H(3_{endo})), 1.57–1.73 (m, 2H), 1.32–1.42 (m, 2H), 1.00 (t, J = 1.9 Hz, 2H; H(4')), 0.90 (s, 3H; H(10)), 0.80 (t, J = 1.9 Hz, 2H; H(9)), 0.69 (s, 3H; H(8)). **^{13}C nmr (CDCl$_3$, 75 MHz):** δ 218.9, 59.4, 48.7, 47.8, 45.2, 34.0, 29.4, 17.2, 15.3 (t, $^1J_{^{13}C-^2H}$ = 19.0 Hz), 14.9 (t, $^1J_{^{13}C-^2H}$ = 18.9 Hz), 9.9.

***endo*-3-Bromo-9-deuterio-4-(deuteriomethyl)camphor (22)**

To a solution of 9-deuterio-4-(deuteriomethyl)camphor (**21**) (1.1587 g, 6.8857 mmol) in glacial acetic acid (4.5 mL) was added a solution of bromine (1.5 mL, 4.8 g, 15 mmol) in glacial acetic acid (1.5 mL). The reaction mixture was heated at 80 °C for 18 h and was then poured into ice-cold, saturated aqueous sodium bisulfite solution (20 mL). The aqueous mixture was extracted with Et_2O (3 × 25 mL) and the combined extracts washed successively with saturated aq. $NaHSO_3$ (1 × 50 mL), $NaHCO_3$ (3 × 50 mL), water (4 × 50 mL), and brine (2 × 50 mL). The organic solution was then dried over anhydrous $MgSO_4$ and concentrated under reduced pressure to provide a viscous brown syrup. Subsequent purification by flash column chromatography (5% Et_2O–pet. ether) yielded *endo*-3-bromo-9-deuterio-4-(deuteriomethyl)camphor (**22**) as white crystals (0.8125 g, 48%). **^{1}H nmr (CDCl$_3$, 400 MHz):** δ 4.28 (d, J = 1.4 Hz, 1H; H(3_{exo})), 2.00–2.10 (m, 1H; H(5_{exo})), 1.48–1.67 (m, 2H), 1.33–1.42 (m, 1H), 0.99 (t, J = 1.9 Hz, 3H; H(4')), 0.97 (s, 3H; H(10)), 0.95 (t, J = 1.9 Hz, 3H; H(9)), 0.78 (s, 3H; H(8)). **^{13}C nmr (CDCl$_3$, 75 MHz):** δ 212.3 (C(2)), 60.4, 59.0, 50.8, 47.0, 30.1, 29.1, 17.4, 16.9 (t, $^1J_{^{13}C-^2H}$ = 19.0 Hz), 13.5 (t, $^1J_{^{13}C-^2H}$ = 19.3 Hz). **EIMS *m/z* (rel intensity):** 248/246 (M^+; 11.0/11.6), 167 ($(M - Br)^+$; 100), 139 (90.9). **Exact mass** calcd for $C_{11}H_{15}BrD_2O$: 246.0586/248.0566, found 246.0596/248.0573.

***endo*-3,9-Dibromo-9-deuterio-4-(bromodeuteriomethyl)camphor (23)**

To an ice-cold solution of *endo*-3-bromo-9-deuterio-4-(deuteriomethyl)camphor (**22**; 1.6246 g, 6.5727 mmol) in chlorosulfonic acid (5.0 mL) was added bromine (0.76 mL, 2.4 g, 15 mmol) in one portion. The reaction mixture was stirred at 0 °C for 1 min and at room temperature for 15 h and then poured cautiously onto ice (~25 mL) containing saturated aq $NaHSO_3$ solution (~25 mL). The precipitated solid was collected by suction filtration, re-dissolved in diethyl ether (100 mL), and then washed successively with saturated aq. $NaHSO_3$ (1 × 50 mL), neutralized with saturated aq. $NaHCO_3$ (3 × 100 mL), and washed with brine (3 × 100 mL). Solvent removal under reduced pressure yielded crude product as an off-white powder. Subsequent purification by flash column chromatography (15% Et_2O–pet. ether) provided *endo*-3,9-dibromo-9-deuterio-4-(bromodeuteriomethyl)camphor (**23**) as colorless needles (0.9845 g, 63%). **^{1}H nmr (CDCl$_3$, 400 MHz):** δ 4.92 (d, J = 2.3 Hz, 1H; H(3_{exo})), 4.01/3.48 (bs, 1H; H(4')), 3.70/3.41 (bs, 1H; H(9)), 2.19 (ddd, J = 13.5, 9.7, 4.0 Hz, 1H; H(5_{endo})), 1.82 (dddd, J = 13.5, 13.5, 5.0, 2.3 Hz, 1H; H(5_{exo}), 1.70 (ddd, J = 13.5, 13.5, 3.9 Hz, 1H; H(6_{exo})), 1.52 (ddd, J = 13.5, 9.7, 5.0 Hz, 1H; H(6_{endo})), 1.24 (s, 3H; H(8)), 1.03 (s, 3H; H(10)). **^{13}C nmr (CDCl$_3$, 75 MHz):** δ 208.0, 61.1, 55.4, 54.1, 50.4, 35.7 (t, $^1J_{^{13}C-^2H}$ = 23.5 Hz), 31.1 (t, $^1J_{^{13}C-^2H}$ = 23.4 Hz), 29.6, 28.2, 16.7, 10.4. **EIMS *m/z* (rel intensity):** 408/406/404/402 (M^+;

1.4/4.5/5.8/2.2), 327/325/323 ((M – Br)$^+$; 47.8/100/52.8), 299/297/295 (4.6/10.7/5.4). **Exact mass** calcd for $C_{11}H_{13}Br_3D_2O$: 401.8795/403.8775/405.8755/ 403.8735, found 401.8778/403.8782/405.8763/ 407.8748.

9-Bromo-9-deuterio-4-(bromodeuteriomethyl)camphor (24)

To a solution of *endo*-3,9-dibromo-9-deuterio-4-(bromodeuteriomethyl)camphor (**23**; 0.9375 g, 2.315 mmol) in 2:1 HOAc–Et_2O (6.0 mL) at 0 °C was added zinc dust (0.3813 g, 5.832 mmol) in one portion. The reaction was allowed to proceed at 0 °C for 3.0 h. Solid materials in the reaction mixture were removed by filtration. The filtrate was diluted with Et_2O (~100 mL), washed successively with water (3 × 50 mL), saturated aqueous $NaHCO_3$ (1 × 50 mL), and brine (2 × 50 mL), and dried over anhydrous $MgSO_4$. Removal of solvent under reduced pressure yielded a golden-yellow product that was purified further by radial chromatography (2 mm plate; 5% Et_2O–pet. ether or 2.5% EtOAc–pet. ether) to yield 9-bromo-9-deuterio-4-(bromodeuterio)camphor (**24**) as a white solid (0.6115 g, 82%). **^{1}H nmr (CDCl$_3$, 400 MHz):** δ 3.90/3.53 (bs, 1H; H(4')), 3.56/3.26 (bs, 1H; H(9)), 2.29 (dd, J = 8.5, 2.6 Hz, 1H; H(3_{exo})), 2.26 (d, J = 8.5 Hz, 1H; H(3_{endo})), 1.82–1.96 (m, 2H), 1.65–1.75 (m, 1H), 1.43–1.53 (m, 1H), 0.99 (s, 3H; H(8)), 0.95 (s, 3H; H(10)). **^{13}C nmr (CDCl$_3$, 75 MHz):** δ 212.9 (C(2)), 61.6, 51.7, 50.9, 47.4, 35.8 (t, $^1J_{^{13}C-^2H}$ = 19.1 Hz), 35.6 (t, $^1J_{^{13}C-^2H}$ = 21.4 Hz), 31.6, 28.1, 15.1, 10.4; **EIMS *m/z* (rel intensity):** 328/326/324 (M^+; 18.5/38.4/21.0), 284/282/280 (10.6/22.2/12.1), 247/245 ((M – Br)$^+$; 87.7/93.2). **Exact mass** calcd for $C_{11}H_{14}Br_2D_2O$: 323.9691/325.9671/327.9651, found 323.9684/ 325.9677/327.9640.

Regenerated 9-Deuterio-4-(deuteriomethyl)camphor (21)

To a solution of 9-bromo-9-deuterio-4-(bromodeuteriomethyl)camphor (**24**; 101 mg, 0.310 mmol) in dry benzene (5.0 mL) was added AIBN (0.110 g, 66.7 μmol) and then tributyltin hydride (205 μL, 221 mg, 0.759 mmol). The reaction mixture was refluxed for 2 h after which it was cooled to room temperature. The solvent was removed under reduced pressure to yield an oily residue that was purified directly by flash column chromatography (1.5% Et_2O–pet. ether) to afford 9-deuterio-4-(deuteriomethyl)camphor (**21**) as white crystals (33.5 mg, 64%).

9-Bromo-4-(bromomethyl)camphorquinone (25)

Selenium dioxide (21.4 g, 0.193 mol) was added, in portions, to a stirred solution of 9-bromo-4-(bromomethyl)camphor (**12**; 11.3 g, 0.0349 mol) in acetic anhydride (21 mL). The grey mixture was heated with stirring at 130–140 °C for 16 h, cooled, and filtered through a Celite® pad. The Celite® pad was washed with ether (200 mL) and the filtrate was washed with water (3 × 250 mL), neutralized with aq. $NaHCO_3$ (1 × 250 mL), washed with brine (2 × 250 mL), dried over anhydrous $MgSO_4$. Removal of solvent yielded a yellow solid that was purified by flash column chromatography (30% Et_2O–pet. ether) to provide 9-bromo-4-(bromomethyl)camphorquinone (**25**) as bright yellow crystals (7.0 g, 59%); mp 94–96 °C . **^{1}H nmr (CDCl$_3$, 400 MHz):** 3.80 (d, J = 11.7 Hz, 1H; H(4')), 3.75 (d, J = 11.0 Hz, 1H; H(9)), 3.73 (d, J = 11.7 Hz, 1H; H(4')), 3.55 (d, J = 11.0 Hz, 1H; H(9)), 2.23–2.33 (m, 1H), 1.93–2.04 (m, 1H), 1.82–1.92 (m, 1H), 1.70 (m, 1H), 1.24 (s, 3H; H(8)), 1.08 (s, 3H; H(10)). **^{13}C nmr (CDCl$_3$, 75 MHz):** 201.0 (C(3)),

198.7 (C(2)), 62.1, 60.2, 48.6, 32.8, 28.7, 27.7, 26.8, 17.3, 10.6. **IR ($CHCl_3$):** 2924, 1774, 1750, 1455, 1381, 1262, 1038 cm^{-1} **UV-Vis** (95% EtOH; $c = 9.3 \times 10^{-4}$ M) λ_{max} (log ε): 478 (1.63), 279 (1.38) nm. **EIMS *m/z* (rel intensity)**: 340/338/336 (M^+; 3.2/6.6/3.5), 231/229 (18.7, 19.1), 203/201 (99.2, 100), 189/187 (3.8, 4.4). **Exact mass** calcd for $C_{11}H_{14}Br_2O_2$: 335.9360/337.9340/339.9320, found 335.9356/337.9337/339.9325. **Anal.** Calcd for $C_{11}H_{14}Br_2O_2$: C, 39.08; H, 4.17. Found: C, 39.14; H, 4.23.

Bromoketoacid (26)

To a solution of 9-bromo-4-(bromomethyl)camphorquinone (**25**; 10.3 g, 0.0305 mol) in spectro grade methanol (300 mL) was added, dropwise over 10 min, aqueous KOH solution [KOH (10.3 g), H_2O (60 mL)]. After stirring 20 min, the pale yellow solution was acidified with 6 M HCl, extracted with ethyl acetate (6 × 200 mL), and the organic extracts washed with water (4 × 1 L) and brine (4 × 1 L) and dried over anhydrous $MgSO_4$. Removal of solvent yielded bromoketoacid (**26**) as a pale yellow syrup (6.9 g, 83%). This product was used without further purification in the subsequent preparation of bromoketoester (**30**). **^{1}H nmr ($CDCl_3$, 300 MHz):** 9.05 (bs, 1H, CO_2H), 4.96–5.01 (m, 2H, $=CH_2$), 3.64 (d, J = 9.8 Hz, 1H; $-CH_2Br$), 3.50 (d, J = 9.8 Hz, 1H; $-CH_2Br$), 2.30–2.73 (m, 3H), 1.60–1.80 (m, 1H), 1.36 (s, 3H; CH_3), 1.21 (s, 3H; CH_3). **IR (neat)**: 2600-3500 (br), 1740, 1706 cm^{-1}

Bromoketoester (27)

To a solution of bromoketoacid (**26**; 6.9300 g, 0.0252 mol) in DMF (125 mL) was added anhydrous K_2CO_3 (8.7021 g, 0.0630 mol) in one portion. The mixture was stirred for 1 h, after which methyl iodide (4.2 mL, 9.6 g, 0.068 mol) was added via syringe. The cloudy mixture was stirred for two hours, diluted with ether (500 mL) and the reaction mixture washed with water (3 × 500 mL) and brine (2 × 500 mL) and dried over anhydrous $MgSO_4$. Removal of solvent yielded a yellow-brown oil that was purified by flash column chromatography (10% Et_2O–pet. ether) to provide bromoketoester **27** as a colorless oil (6.0010 g, 82%). **^{1}H nmr ($CDCl_3$, 400 MHz):** 4.96-5.00 (m, 2H; $=CH_2$), 3.79 (s, 3H, $-COCH_3$), 3.59 (d, J = 10.3 Hz, 1H; $-C\underline{H}_AH_BBr$), 3.47 (d, J = 10.3 Hz, 1H; $-CH_A\underline{H}_BBr$), 2.34–2.62 (m, 2H), 1.71 (ddd, J = 6.2, 4.0, 2.5 Hz, 2H), 1.39 (s, 3H; CH_3), 1.22 (s, 3H; CH_3). **^{13}C nmr ($CDCl_3$, 75 MHz):** 200.4, 164.5, 154.5, 108.8, 58.7, 52.4, 51.9, 40.1, 32.9, 29.1, 21.4, 18.3. **IR ($CHCl_3$):** 2955, 1738, 1704 , 1456, 1435, 1378, 1289, 1027 cm-1 **EIMS *m/z* (rel intensity):** 290/288 (M^+; 0.2/0.2), 231/201 (83.4/84.7), 121 (100). **Exact mass** calcd for $C_{12}H_{17}BrO_3$: 288.0361/290.0341, found 288.0365/290.0342. **Anal.** Calcd for $C_{12}H_{17}BrO_3$: C, 49.84; H, 5.93. Found: C, 49.90; H, 5.96.

Bromohydroxyester (28)

To an ice-cold solution of bromoketoester (**27**; 2.0037 g, 6.932 mmol) in methanol (85 mL) was added $NaBH_4$ (0.1201 g, 3.174 mmol) in small portions over 5 min. After stirring an additional 5 min at 0 °C , the solution was neutralized with 1 M HCl, diluted with 100 mL brine and the aqueous mixture was extracted with ether (3 × 100 mL). The combined organic extracts were washed with water (2 × 250 mL) and brine (2 × 250 mL), and dried over anhydrous $MgSO_4$. Removal of solvent yielded a pale yellow syrup that was purified by flash column chromatography (30% Et_2O–pet. ether) to provide bromohydroxyester (**28**) as a white semi-solid (1.5405 g, 76%). **^{1}H nmr ($CDCl_3$, 400 MHz)**: 5.37 (dd, J = 2.3, 2.3 Hz, 1H; $=C\underline{H}_AH_B$), 4.86 (dd, J =

2.3, 2.3 Hz, 1H, =$CH_A\underline{H}_B$), 4.25/4.41 (major diastereomer/minor diastereomer) (d, J = 6.0 Hz, 1H; -C<u>H</u>(OH)), 4.18/3.96 (d, J = 10.8 Hz, 1H; Br$C\underline{H}_AH_B$), 3.76/3.72 (s, 3H; -CO_2Me), 3.56/3.39 (d, J = 10.8 Hz, 1H; Br$CH_A\underline{H}_B$), 2.93/2.98 (d, J = 5.4 Hz, 1H; –OH), 2.43–2.52 (m, 1H), 2.30–2.40 (m, 1H), 1.82–1.97 (m, 1H), 1.36–1.45 (m, 1H), 1.31/1.24 (s, 3H; –CH_3), 1.13/0.85 (s, 3H; –CH_3). **IR ($CHCl_3$)**: 3506, 2954, 1732, 1439, 1373, 1254, 1146, 1084 cm^{-1} **EIMS *m/z* (rel intensity)**: 245/243 ($(M - OCH_3)^+$; 0.4/0.6), 203/201 (18.2), 151 (17.2), 133 (14.3), 121 (100.0). **Exact mass** calcd for $C_{11}H_{16}BrO_2$ ($M - OCH_3)^+$: 243.0381/245.0361, found 243.0385/245.0365.

Bromoacetoxyester (29)

Acetic anhydride (1.00 mL, 1.08 g, 10.6 mmol) was added dropwise over 5 min to a solution of bromohydroxyester (**28**; 1.1970 g, 4.11 mmol) and 4-dimethylaminopyridine (DMAP; 0.6010 g, 4.92 mmol) in pyridine (4.5 mL). The mixture was stirred for 1.5 hr, diluted with ether (50 mL) and the organic solution, washed with water (2 × 150 mL), neutralized with 1 M HCl (1 × 150 mL), washed with brine (2 × 150 mL), and dried over anhydrous $MgSO_4$. Removal of solvent and yielded a yellow syrup that was purified by flash column chromatography (25% Et_2O–pet. ether) to provide bromoacetoxyester (**29**) as a colorless syrup (0.8692 g, 63%). **^{1}H nmr ($CDCl_3$, 400 MHz)**: 5.25 (dd, J = 2.3, 2.3 Hz, 1H; =$C\underline{H}_AH_B$), 4.94 (t, J = 2.3, 2.3 Hz, 1H; =$CH_A\underline{H}_B$), 4.87 (s, 1H; -C<u>H</u>(OAc)), 3.80 (d, J = 10.4 Hz, 1H; –$C\underline{H}_AH_B$Br), 3.71/3.70 (major/minor diastereomers; s, 3H; –CO_2Me), 3.54 (d, J = 10.4 Hz, 1H; –$CH_A\underline{H}_B$Br), 2.37–2.52 (m, 2H), 2.13/2.15 (major/minor diastereomers; s, 3H, C(O)C<u>H</u>$_3$), 1.90 (ddd, J = 13.6, 7.8, 5.0 Hz, 1H), 1.40–1.47 (m, 1H), 1.17/1.18 (s, 3H, –CH_3), 1.04/1.00 (s, 3H; –CH_3). **^{13}C nmr ($CDCl_3$, 75 MHz)**: 170.0 (C=O), 169.5 (C=O), 155.7, 108.6, 76.8, 51.9, 51.1, 48.9, 41.0, 33.0, 28.6, 21.3, 20.5, 16.5. **IR ($CHCl_3$)**: 2977, 1747, 1653, 1436, 1374, 1236, 1170, 1057, 1011 cm^{-1} **EIMS *m/z* (rel intensity)**: 301/303 ($(M - OCH_3)^+$; 0.1/0.1), 203/201 (28.5/29.7), 193 (25.1), 133 (45.1), 121(100.0). **Exact mass** calcd for $C_{13}H_{18}BrO_3$ ($M - OCH_3)^+$: 301.0436/303.0416, found 301.0432/303.0413. **Anal.** Calcd for $C_{14}H_{21}BrO_4$: C, 50.46; H, 6.35. Found: C, 50.55; H, 6.40.

Bromoester (30)

A solution of bromoacetoxyester (**29**; 0.3529 g, 1.06 mmol) in HMPA (1.60 mL, 1.65 g, 9.20 mmol) and 1:1 MeOH–THF (2.2 mL) was transferred[35] over 10 min, by cannula, to an ice-cold, dark blue solution of samarium(II) iodide in THF[33] (~0.1 M; 29.5 mL, 3 mmol). The resulting dark purple mixture was stirred at 0 °C for 3 h and then exposed to air for 5 min. The yellow reaction mixture was diluted with ether (30 mL), washed with water (2 × 100 mL) and brine (2 × 100 mL) and dried over anhydrous $MgSO_4$. Removal of solvent yielded a yellow syrup that was purified by flash column chromatography (30% Et_2O–pet. ether) to provide bromoester (**30**) as a colorless oil (0.1186 g, 41%). **^{1}H nmr ($CDCl_3$, 400 MHz)**: 4.95 (dd, J = 2.1, 2.1 Hz, 1H; =$C\underline{H}_AH_B$), 4.83 (dd, J = 2.1, 2.1 Hz, 1H; =$CH_A\underline{H}_B$), 3.63 (s, 3H; -CO_2Me), 3.49 (d, J = 10.4 Hz, 1H; Br$C\underline{H}_AH_B$), 3.44 (d, J = 10.5 Hz, 1H, Br$CH_A\underline{H}_B$), 2.58 (d, J = 13.5 Hz, 1H; $MeO_2CC\underline{H}_AH_B$), 2.38–2.46 (m, 2H), 2.27 (d, J = 13.6 Hz, 1H, $MeO_2CCH_A\underline{H}_B$), 1.81–1.88 (m, 1H), 1.58–1.67 (m, 1H), 1.09 (s, 3H; –CH_3), 1.07 (s, 3H; –CH_3). **^{13}C nmr ($CDCl_3$, 75 MHz)**: 172.9, 156.2, 108.3, 51.2, 50.9, 46.6, 41.8, 41.3, 33.6, 28.6, 20.6, 19.8. **IR ($CHCl_3$)**: 2952, 1737, 1651, 1436, 1375, 1202, 1167, 1015 cm^{-1} **EIMS *m/z* (rel intensity)**: 276/274 (M^+; 0.4/0.3), 202/200 (11.4/10.5), 181 (13.9), 122 (11.34),

121 (100.0). **Exact mass** calcd for $C_{12}H_{19}BrO_2$: 274.0569/276.0549, found 274.0570/276.0544. **Anal.** Calcd for $C_{12}H_{19}BrO_2$: C, 52.38; H, 6.96. Found: C, 52.48; H, 6.70.

REFERENCES

1. Dadson, W.M.; Lam, M.; Money, T.; Piper, S.E. *Can. J. Chem.* **1983**, *61*, 343.
2. Rettig, S.; Trotter, J. *Acta Cryst.* **1986**, *C42*, 1452.
3. *cf.* Nishikawa, M.; Hagiwara, H. *J. Pharm. Soc., Jpn.* **1954**, *74*, 76; *Chem. Abstr.* **1955**, *49*, 1596a.
4. *cf.* Nishikawa, M.; Hagiwara, H. *J. Pharm. Soc., Jpn.* **1954**, *74*, 81; *Chem. Abstr.* **1955**, *49*, 1596h.
5. Hutchinson, J.H.; Money, T.; Piper, S.E. *Can. J. Chem.* **1986**, *64*, 854.
6. Money, T. In *Organic Synthesis: Theory and Application*; Hudlicky, T., Ed.; JAI: Greenwich, CT, USA: 1996; Vol. 3, pp 1–83.
7. Hutchinson, J.H.; Money, T. *Can. J. Chem.* **1985**, *63*, 3182.
8. Hutchinson, J.H.; Money, T.; Piper, S.E. *Can. J. Chem.* **1986**, *64*, 1404.
9. (a) Rowley, M.; Tsukamoto, M.; Kishi, Y. *J. Am. Chem. Soc.* **1989**, *111*, 2735.
   (b) Rowley, M.; Kishi, Y. *Tetrahedron Lett.* **1988**, *29*, 4909.
10. Williams, D.R.; Coleman, P.J.; Henry, S.S. *J. Am. Chem. Soc.* **1993**, *115*, 11654.
11. Money, T.; Richardson, S.R.; Wong, M.K.C. *Chem. Commun.* **1996**, 667.
12. Money, T.; Wong, M.K.C. *Tetrahedron* **1996**, *52*, 6307.
13. Hutchinson, J.H.; Money, T. *Can. J. Chem.* **1987**, *65*, 1.
14. Clase, J.A.; Money, T. *Synthesis* **1989**, 934.
15. Clase, J.A.; Money, T. *Can. J. Chem.* **1992**, *70*, 1537.
16. Money, T.; Richardson, S.R.; Wong, M.K.C., unpublished results; *cf.* Richardson, S.R. M.Sc. Thesis, The University of British Columbia, Vancouver, BC, Canada; October, 1993.
17. Clase, J.A.; Li, D.L.F.; Lo, L.; Money, T. *Can. J. Chem.* **1990**, *68*, 1829.
18. Money, T.; Palme, M.H. *Tetrahedron: Asymmetry* **1993**, *4*, 2363.
19. Previous synthetic routes to the lanostane and euphane classes of triterpenoids have been reported by Barton[20], Woodward[20], van Tamelen[21], Reusch[22], Johnson[23], Corey[24] and their respective co-workers.
20. Woodward, R.B.; Patchett, A.A.; Barton, D.H.R.; Ives, D.A.J.; Kelly, R.B. *J. Chem. Soc.* **1957**, 1131.
21. van Tamelen, E.E.; Anderson, R.J. *J. Am. Chem. Soc.* **1972**, *94*, 8225 and references cited.
22. Kolaczkowski, L.; Reusch, W. *J. Org. Chem.* **1985**, *50*, 4766 and references cited.
23. Bartlett, W.R.; Johnson, W.S.; Plummer, M.S.; Small, V.R., Jr. *J. Org. Chem.* **1990**, *55*, 2215.
24. Corey, E.J.; Lee, J.; Liu, D.R. *Tetrahedron Lett.* **1994**, *35*, 9149.
25. Forster, M.O. *J. Chem. Soc.* **1902**, *81*, 264.
26. Burgess, H. *J. Chem. Soc.* **1924**, *125*, 2375.
27. Li, D.L.F. M.Sc. Thesis, The University of British Columbia, Vancouver, BC, Canada; March, 1989.
28. Rettig, S.; Trotter, J. The University of British Columbia, Vancouver, BC, Canada; unpublished results.
29. Cachia, P.; Darby, N.; Eck, C.R.; Money, T. *J. Chem. Soc., Perkin Trans. 1* **1976**, 359.
30. Phillips, S.E.V.; Trotter, J. *Acta Cryst.* **1977**, *B33*, 200.
31. Money, T. *Nat. Prod. Rep.* **1985**, *2*, 253.
32. Kusada, K.; Inanaga, J.; Yamaguchi, M. *Tetrahedron Lett.* **1989**, *30*, 2945.
33. (a) *cf.* Molander, G.A. *Chem. Rev.* **1992**, *92*, 29.
   (b) *cf.* Molander, G.A.; Hahn, G. *J. Org. Chem.* **1986**, *51*, 1135.
34. *cf.* Soderquist, J.A. *Aldrichimica Acta* **1991**, *24*, 15.
35. *cf.* Shriver, D.F.; Drezdon, M.A. *The Manipulation of Air-Sensitive Compounds*, 2nd Ed.; Wiley-Interscience: New York, 1986.

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