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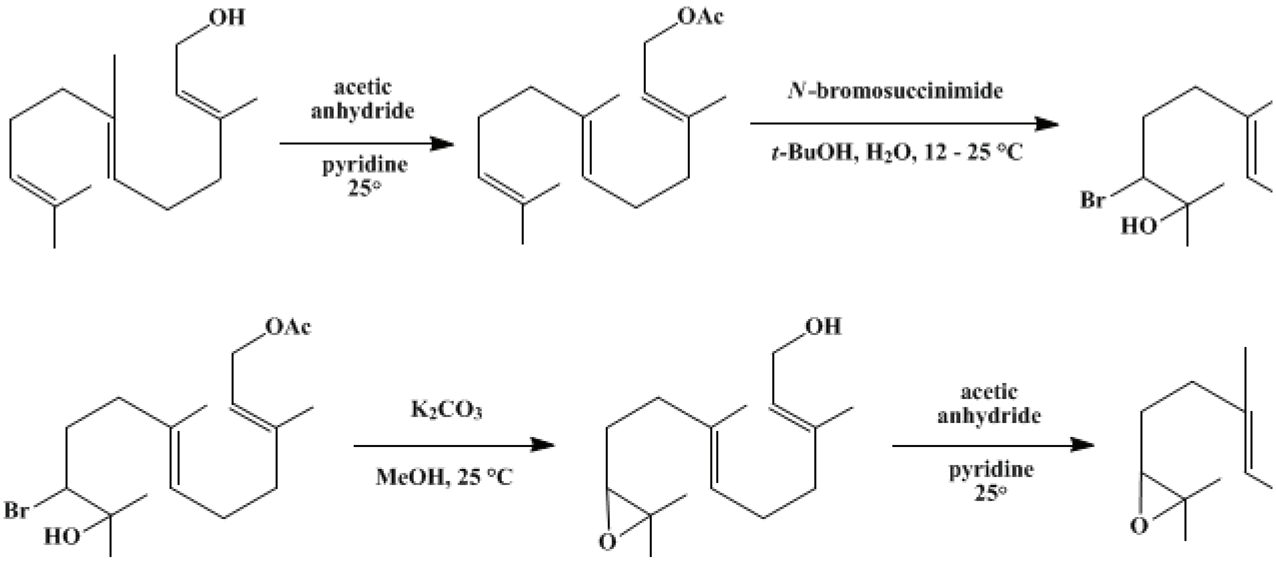
SELECTIVE EPOXIDATION OF TERMINAL DOUBLE BONDS: 10,11-EPOXYFARNESYL ACETATE

[2,6-Nonadien-1-ol, 9-(3,3-dimethyloxiranyl)-3,7-dimethyl-, acetate, (*E*,*E*)-]



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1. Procedure

A. ***Farnesyl acetate***. A solution of 25 g. (0.11 mole) of farnesol (Note 1) in 40 ml. of dry pyridine (Note 2) is prepared in a stoppered, 250-ml. Erlenmeyer flask, and 40 ml. of acetic anhydride is added in four portions over a 15-minute period. The mixture is stirred well, allowed to stand for 6 hours then poured onto 250 g. of ice. Water is added (400 ml.), and the mixture is extracted with five 100-ml. portions of petroleum ether (b.p. 60–68°). The organic extracts are combined and washed in succession with two 50-ml. portions each of water, 5% sulfuric acid, and saturated aqueous sodium hydrogen carbonate, dried over anhydrous magnesium sulfate (*ca.* 50 g.), and concentrated on a rotary evaporator, yielding 28–29 g. (94–98%) of farnesyl acetate as a colorless oil (Note 3).

B. 10-*Bromo*-11-*hydroxy*-10,11-*dihydrofarnesyl acetate*. Farnesyl acetate (29 g., 0.11 mole) is dissolved in 1 l. of *tert*-butyl alcohol (Note 4) contained in a 3-l. Erlenmeyer flask. Water is added (500 ml.), and the solution is cooled to about 12° with an external ice water bath. Maintaining this temperature, rapid magnetic stirring is begun, and more water is added until a saturated solution is obtained. The second addition of water may be rapid initially, but the saturation point must be approached carefully, like the end point of a titration. A total of about 1200 ml. of water is required for the specified quantities of farnesyl acetate and *tert*-butyl alcohol. The solution must remain clear and homogeneous at about 12°, and if the saturation point is accidentally passed by adding too much water, *tert*-butyl alcohol should be added to remove the turbidity.

External cooling is discontinued, and 21.4 g. (0.120 mole) of *N*-bromosuccinimide (Note 5) is added. Stirring is continued until all of the solid is dissolved (*ca.* 1 hour). The resulting solution, which may be pale yellow, is concentrated with a rotary evaporator (bath temperature 40–45°) to a volume of about 300 ml. and extracted with five 120-ml. portions of diethyl ether. The combined ether extracts are dried over anhydrous magnesium sulfate (20–50 g.), and removal of solvent at reduced pressure provides an oil, which is purified by column chromatography on silica gel (Note 6). The pure bromohydrin acetate is obtained as a colorless oil in amounts of up to 26 g., a 65% yield based on farnesyl acetate (Note 7) and (Note 8).

C. 10,11-*Epoxyfarnesyl acetate*. The bromohydrin acetate prepared in Part B is dissolved in 300 ml. of methanol, the solution is placed in a 500-ml. flask, and excess solid potassium carbonate (three times the molar amount of bromohydrin acetate) is added (Note 9). The mixture is stirred for 12 hours and then concentrated to *ca.* 100 ml. on a rotary evaporator (bath at 40–45°). Water is added (200 ml.), and the mixture is extracted with four 100-ml. portions of petroleum ether (b.p. 60–68°). The combined extracts are dried over anhydrous magnesium sulfate (*ca.* 40 g.) and evaporated, leaving 10,11-epoxyfarnesol as a colorless oil (Note 10).

This material is acetylated with 35 ml. of pyridine and 35 ml. of acetic anhydride for 6 hours at room temperature. The mixture is poured onto 250 g. of ice and extracted with five 75-ml. portions of ether. The combined ether extracts are washed successively with three 10-ml. portions each of saturated aqueous sodium hydrogen carbonate and water then dried over magnesium sulfate. It is important not to use strong acids such as hydrochloric or sulfuric to remove pyridine, as was done in Part A, since they can destroy the acid-sensitive product.

Concentration of the ethereal solution at reduced pressure gives the epoxyacetate as a colorless oil more viscous than water. The overall yield based on farnesyl acetate is near 60% (Note 11). This material is reasonably pure if the preparation has been executed carefully, but it can be further purified by column chromatography (Note 12) or distillation (Note 13).

2. Notes

1. Farnesol was obtained from Fluka AG (Buchs, CH9470, Switzerland) as a mixture of 65% (*E*),(*E*)- and 35% (*Z*),(*E*)-isomers. It is also available from the Aldrich Chemical Company, Inc. This procedure works equally well with pure (*E*),(*E*)-farnesol, which may be obtained from the above mixture by careful distillation, at reduced pressure, through a Nester-Faust Teflon spinning-band column.
2. Pyridine was distilled from sodium hydroxide.
3. IR (neat) cm.$^{-1}$: 1740, 1240; ^{1}H NMR (CCl_4), δ (multiplicity, coupling constant J in Hz., number of protons, assignment): 2.00 (s, 3H, O_2CCH_3), 4.46 (d, $J = 7$, 2H, CH_2O), 4.49–5.4 (m, 3H, olefinic *H*).
4. Tetrahydrofuran or glyme work equally well in place of *tert*-butyl alcohol as a co-solvent, but should be distilled under dry nitrogen from lithium aluminum hydride[2] or sodium and benzophenone [*Org. Synth.*, **Coll. Vol. 5**, 201 (1973)] prior to use, to destroy peroxides which may be present.
5. The *N*-bromosuccinimide should be nearly white and uncontaminated by free bromine. If necessary, it may be recrystallized from hot water and stored in a refrigerator.
6. The submitters mixed active anhydrous silica gel with water (12% w/w) and stored it in a sealed container for at least 24 hours prior to use. A ratio of 60–80 g. of silica gel per gram of crude product was used for column chromatographic separations, and a column was chosen that would give a 10:1 height:diameter ratio of adsorbent. Columns were wet-packed with distilled petroleum ether (b.p. 60–68°), and after the crude product had been applied a step-gradient was run through rapidly: 2% ether, 5% ether, and 10% ether (v/v) in petroleum ether. The column was then eluted with 20% v/v ether in petroleum ether until the bromohydrin acetate was obtained.
The checkers obtained roughly 30 g. of crude product in each run. Freshly opened Woelm silica gel (obtained from ICN Pharmaceuticals, 26201 Miles Ave., Cleveland, Ohio 44128) was deactivated as above, and 1800 g. was wet-packed with petroleum ether in a 65-mm.-internal-diameter column. In the first run the column was eluted as above, but a considerable amount of solvent was required to collect the product. Therefore, in the second run the crude product was applied to the column as a solution in petroleum ether, and 1-l. portions of 20% v/v ether:petroleum ether, 30% ether, 40% ether, 50% ether, 60% ether, and 70% ether were run through. None of these six fractions contained a significant weight of material. Elution with 2 l. of 80% v/v ether:petroleum ether provided the bromohydrin acetate.
Fractions may be monitored by TLC on silica gel, developing with 10% v/v ethyl acetate in hexane and visualizing with iodine vapor. The following R_f values were observed: farnesol, 0.07; farnesyl acetate, 0.35; bromohydrin acetate, 0.20.
7. In each of two runs, the checkers obtained 25 g. (63% yield).
8. IR (neat) cm.$^{-1}$: 3520, 3450, 1740, 1235; ^{1}H NMR (CCl_4), δ (multiplicity, coupling constant J in Hz., number of protons, assignment): 1.32 [s, 6H, $OC(CH_3)_2$], 2.00 (s, 3H, O_2CCH_3), 3.7–4.0 (m, 1H, $CHBr$),

4.50 (d, $J = 7$, 2H, CH_2O), 4.9–5.5 (m, 2H olefinic H).

9. Using a smaller amount of K_2CO_3 made the reaction much slower and did not avoid or reduce the accompanying loss of the acetate group. Pyridine at room temperature is not sufficiently basic to form the epoxide. Other bases were not tested.

10. IR (neat) cm.$^{-1}$: 3450, 2940, 1450, 1375; ^{1}H NMR (CCl_4), δ (multiplicity, coupling constant J in Hz., number of protons, assignment): δ 1.25 and 1.29 [2s, 6H, $OC(CH_3)_2$], 2.55 (t, $J = 6$, 1H, OCH), 3.97 (d, $J = 7$, 2H, OCH_2), 5.0–5.5 (m, 2H, olefinic CH).

11. In each of two runs, the checkers obtained 19 g. (61% yield). IR (neat) cm.$^{-1}$: 2950, 1740, 1380, 1235; ^{1}H NMR (CCl_4), δ (multiplicity, coupling constant J in Hz., number of protons, assignment): 1.21 and 1.23 [2s, 6H, $OC(CH_3)_2$], 1.97 (s, 3H, O_2CCH_3), 2.50 (t, $J = 6$, 1H, OCH), 4.48 (d, $J = 7$, 2H, OCH_2), 5.0–5.5 (m, 2H, olefinic CH).

12. Deactivation of silica gel and preparation of the column is carried out as in (Note 6), except that the checkers consider 20 g. of silica gel per gram of crude product to be adequate in this case. Running through a gradient of petroleum ether containing increasing amounts of ether, the submitters found that the product was eluted with 15% (v/v) ether, but the checkers found that 25% (v/v) ether was required.

13. The submitters recommend distillation at 100° at less than 0.005 mm. The checkers distilled 1–2 g.-samples at 0.05 mm. (b.p. 113°) and at 0.15 mm. (b.p. 117°), and in both cases a clean product was obtained with high recovery.

3. Discussion

10,11-Epoxyfarnesol was first prepared by van Tamelen, Storni, Hessler, and Schwartz[3] using essentially this procedure, which is based on the findings of van Tamelen and Curphey[4] that *N*-bromosuccinimide in a polar solvent is a considerably more selective oxidant than others tried. This method has been applied to produce terminally epoxidized mono-, sesqui-, di-, and triterpene systems for biosynthetic studies and bioörganic synthesis.[5] It has also been applied successfully in a simple synthesis of tritium-labeled squalene and squalene-2,3-oxide[6] and in the synthesis of *Cecropia* juvenile hormone.[7]

The oxidation procedure described above is intended to illustrate the selectivity that may be achieved using this system for functionalizing only one of several superficially similar double bonds in a molecule. In the case of acyclic terpenes, the yield of the desired terminal monobromohydrin decreases from 75–80% with geraniol ($C_{10}H_{18}O$) to 30–35% with squalene ($C_{30}H_{50}$), due to competing formation of polybromohydrins, allylic bromides, and bromocyclized material. The significant point, however, is that in all cases more than 95% of the monobromohydrin produced results from attack at the terminal double bond. A mechanistic investigation[8] showed that the *N*-bromosuccinimide was not merely providing a source of bromine or hypobromous acid, and that the reaction was promoted by acid and inhibited by base.

References and Notes

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Appendix
Chemical Abstracts Nomenclature (Collective Index Number);
(Registry Number)

silica gel

petroleum ether

tritium-labeled squalene

squalene-2,3-oxide

potassium carbonate (584-08-7)

sulfuric acid (7664-93-9)

ethyl acetate (141-78-6)

methanol (67-56-1)

ether,
diethyl ether (60-29-7)

acetic anhydride (108-24-7)

sodium hydroxide (1310-73-2)

sodium hydrogen carbonate (144-55-8)

bromine (7726-95-6)

nitrogen (7727-37-9)

iodine (7553-56-2)

pyridine (110-86-1)

Benzophenone (119-61-9)

sodium (13966-32-0)

hypobromous acid (13517-11-8)

magnesium sulfate (7487-88-9)

Tetrahydrofuran (109-99-9)

lithium aluminum hydride (16853-85-3)

N-bromosuccinimide (128-08-5)

hexane (110-54-3)

geraniol (106-24-1)

tert-butyl alcohol (75-65-0)

farnesol

10,11-Epoxyfarnesyl acetate,
2,6-Nonadien-1-ol, 9-(3,3-dimethyloxiranyl)-3,7-dimethyl-, acetate, (E,E)- (50502-44-8)

Farnesyl acetate

10,11-epoxyfarnesol

squalene

10-Bromo-11-hydroxy-10,11-dihydrofarnesyl acetate (54795-59-4)

(E),(E)-farnesol