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REGIOSELECTIVE OZONOLYTIC CLEAVAGE OF UNSYMMETRIC CYCLOALKENES

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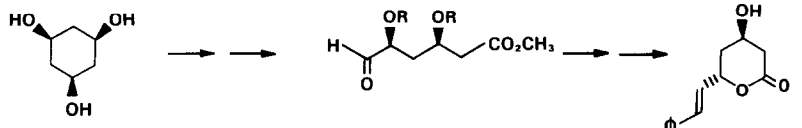
Abstract: Aldehyde 2 was prepared in a one-pot sequence from olefin 12; olefin 6 did not react similarly. Possible reasons for the differences are discussed.

We have recently[1] reported a new synthesis of trans-β-hydroxy-δ-lactone 3, starting from cis-cyclohexane-1,3,5-triol, 1, employing aldehyde 2 as the key intermediate. The symmetrical cis disposition of hydroxy groups in triol 1 was thus effectively utilized for obtaining a single diastereoisomer of lactone 3. A report by Schreiber and co-workers[2] on the ozono-

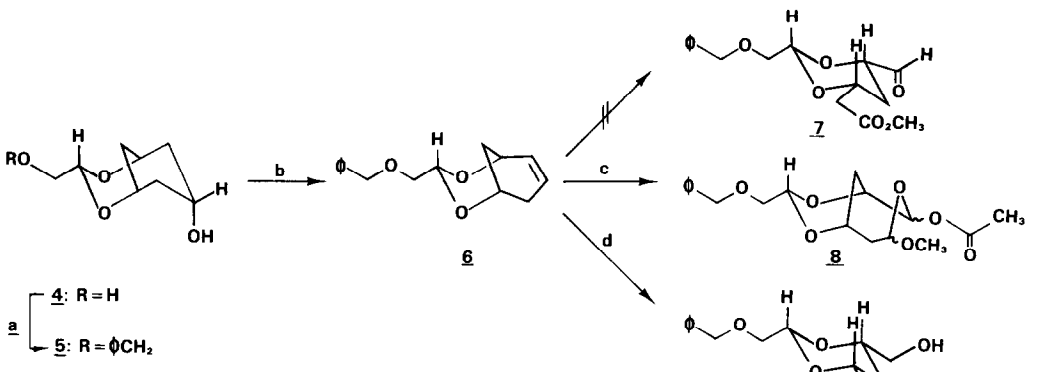


1 2 3

lytic cleavage of cycloalkenes to products with differentiated termini, prompted us to examine the usefulness of unsymmetrical cyclohexenes derived from triol 1 for the regioselective[3] formation of aldehydes 2.

Initially, we chose the bicyclic olefin 6 (see Scheme I) as the substrate for

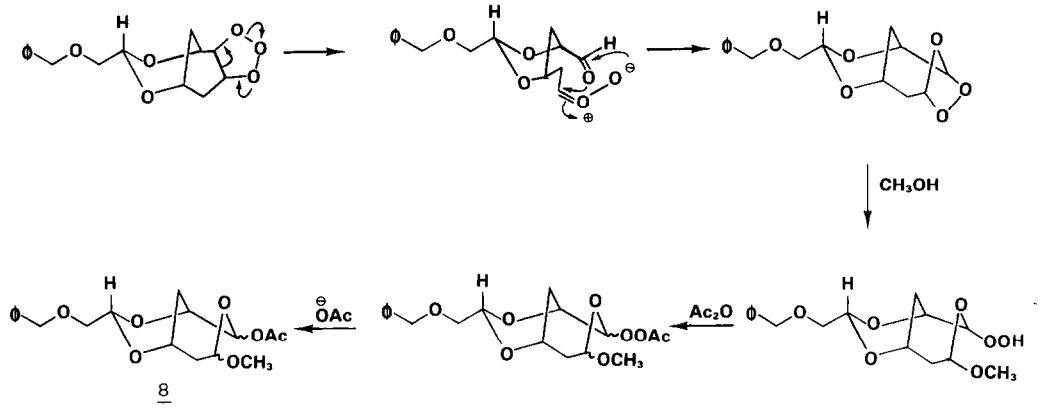
SCHEME I.



a: ΦCH₂Cl, KOH, DMSO; b: CH_3SO_2Cl, pyridine, then KOH, isopropanol; c: O_3, CH_3OH, CH_2Cl_2, $NaHCO_3$, then NEt_3, $(CH_3CO)_2O$, CH_2Cl_2; d: O_3, CH_3OH, CH_2Cl_2, $NaHCO_3$, then $NaBH_4$, CH_3OH.

regioselective ozonolysis; it was obtained as follows. Diol 4 was derived in high yield from triol 1 and glyoxylic acid in two steps following Woodward's methodology.[4] Selective benzylation of the primary hydroxy group in diol 4 was carried out with benzyl chloride and KOH in DMSO. Compound[5,6] 5, on treatment with excess methanesulfonyl chloride in pyridine followed by refluxing in isopropanol/KOH,[4] yielded the desired olefin 6 in high yield. Ozonolysis of olefin 6 in CH_3OH/CH_2Cl_2 buffered with $NaHCO_3$ at -78 °C, followed by treatment with acetic anhydride and triethylamine,[2] gave an isomeric acetal mixture 8 as the major product, instead of the expected aldehyde ester 7. The product can be explained by postulating that a cyclic peracetate acetal is formed, which solvolyzes rather than eliminates acetate (see Scheme II).

SCHEME II.



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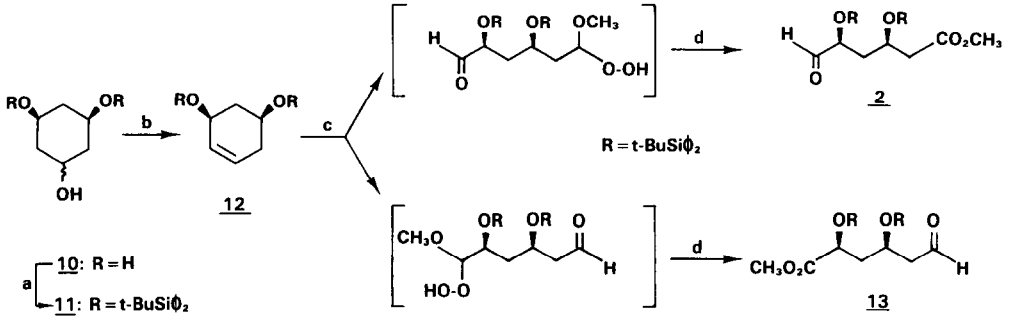
Due to these results, we turned to the monocyclic olefin 12 as a better alternative for the ozonolysis (see Scheme III). It was synthesized in three steps starting from triols 10.

SCHEME III.



a: t-Butyldiphenylsilyl chloride, imidazole, DMF; b: CH_3SO_2Cl, pyridine, then DBU, DMSO, 110 °C; c: O_3, CH_3OH, CH_2Cl_2, $NaHCO_3$; d: NEt_3, $(CH_3CO)_2O$, CH_2Cl_2.

Silylation of triols 10 with two equivalents of t-butylchlorodiphenylsilane (imidazole, DMF) gave a mixture[8] of disilylated products 11. Mesylation of 11 with methanesulfonyl chloride in pyridine followed by heating (110 °C) with DBU in DMSO provided olefin 12 in 60% yield. Ozonolysis[9] of olefin 12 under the conditions mentioned earlier (CH_3OH/CH_2Cl_2, $NaHCO_3$, O_3, then CH_2Cl_2, acetic anhydride, triethylamine) yielded the desired aldehyde ester 2 and its isomer 13 (in the ratio of 7:1) in 75% yield.

Aldehyde 2 was found to be a very useful intermediate in the synthesis of different derivatives of β-hydroxy-δ-lactones, eg., 3, which are potent hypocholesterolemic agents.

ACKNOWLEDGEMENT

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REFERENCES AND NOTES

1. Prasad, K., Repič, O., Tetrahedron Lett., 1984, 2435.

2. Schreiber, S.L., Claus, R. E., Reagan, J., Tetrahedron Lett., 1982, 3867.

3. Based on the induction arguments (ref. 2 and other references cited therein), we anticipated that the oxygen substituent on the allylic carbon will have a greater directing effect in the cleavage of the primary ozonide, compared to the one on the homoallylic carbon.

4. Woodward, R.B., Gosteli, J., Ernest, I., Friary, R.J., Nestler, G., Raman, H., Sitrin, R., Suter, Ch., Whitesell, J.K., J. Am. Chem. Soc., 1973, 95, 6853.

5. The heterocyclic ring in the bicyclic compounds is represented in a boat conformation because NMR experiments observed a large NOE between the acetal hydrogen and the proton at the bridgehead carbon in compound 6. Molecular modeling by computer (PRXBLD program) also suggests the boat conformation. For the sake of clarity, only one enantiomer is depicted for the compounds described in this communication, although most are racemic.

6. All new compounds were characterized by spectroscopic methods and microanalysis. Selected physical data:

Compound 5: oil; IR ($CHCl_3$): 3522 (OH), 3018, 2926, 2406, 1462, 1417, 1322, 1219, 1119, 1032, 972, 917 cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.45 (d, J=15 Hz, 1H), 1.70 (dd, J=5&15 Hz, 2H), 2.45 (bd, J=15 Hz, 2H), 2.77 (m, 1H), 3.50 (d, J=3 Hz, 2H), 4.05 (m, 1H), 4.35 (d, J=12 Hz, 1H), 4.57 (br, 2H), 4.65 (s, 2H), 5.35 (t, J=3 Hz, 1H), 7.25-7.45 (m, 5H); ^{13}C NMR ($CDCl_3$): δ 137.55, 128.23, 127.69, 127.55, 90.31, 73.86, 70.58, 68.51, 65.52, 39.32, 26.87.

Compound 6: oil; ^1H NMR ($CDCl_3$): δ 1.55 (dd, J=3&15 Hz, 1H), 2.18 (m, 1H), 2.36 (m, 1H), 2.65 (m, 1H), 3.42 (m, 2H), 4.40 (m, 1H), 4.55 (m, 1H), 4.56 (dd, J=14 Hz, 2H), 5.30 (t, J=5 Hz, 1H), 5.76 (m, 1H), 6.05 (m, 1H), 7.20-7.40 (m, 5H); ^{13}C NMR ($CDCl_3$): δ 137.84, 129.62, 128.20, 127.84, 127.52, 126.70, 89.67, 73.52, 72.31, 66.49, 63.40, 34.31, 25.26.

Compound 9: oil; ^1H NMR ($CDCl_3$): δ 1.45 (m, 2H), 1.75 (m, 2H), 2.48 (br, 1H), 2.60 (br, 1H), 3.50-4.00 (m, 8H), 4.55 (s, 2H), 4.80 (t, J=5 Hz, 1H), 7.25-7.40 (m, 5H); ^{13}C NMR ($CDCl_3$): δ 137.67, 128.40, 127.82, 99.48, 76.70, 74.96, 73.62, 71.31, 65.35, 59.80, 37.94, 32.39.

Compound 11a (cis OH): mp 109-110 °C; ^1H NMR ($CDCl_3$): δ 1.00 (s, 18H), 1.17-1.59 (m, 4H), 1.95 (m, 3H), 3.00-3.42 (m, 3H), 7.20-7.60 (m, 20H).

Compound 11b (trans OH): oil; ^{1}H NMR ($CDCl_3$): δ 1.00 (s, 18H), 1.20-2.40 (m, 7H), 3.75-4.00 (m, 3H), 7.20-7.72 (m, 20H); ^{13}C NMR ($CDCl_3$): δ 135.72, 134.81, 134.55, 129.59, 129.47, 127.69, 127.46, 66.75, 66.49, 45.58, 41.55, 27.04, 19.13.

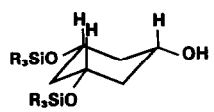
Compound 12: mp 139-140 °C; ^{1}H NMR ($CDCl_3$): δ 1.00 (s, 9H), 1.03 (s, 9H), 1.73 (m, 1H), 2.05 (m, 3H), 3.57 (m, 1H), 4.11 (m, 1H), 5.43 (m, 2H), 7.20-7.62 (m, 20H); ^{13}C NMR ($CDCl_3$): δ 135.83, 135.73, 134.42, 134.32, 131.50, 129.50, 127.50, 125.22, 69.09, 67.74, 42.49, 35.07, 27.00, 19.14.

Compound 2: oil; IR ($CHCl_3$): 1735 cm^{-1} (ester and aldehyde CO); ^{1}H NMR ($CDCl_3$): δ 0.98 (s, 9H), 1.05 (s, 9H), 1.95 (t, J=6 Hz, 2H), 2.33 (d, J=6 Hz, 2H), 3.50 (s, 3H), 4.10 (t, J=6 Hz, 1H), 4.45 (m, 1H), 7.25-7.75 (m, 20H), 9.30 (s, 1H); ^{13}C NMR ($CDCl_3$): δ 201.83, 171.02, 135.81, 134.79, 133.70, 133.38, 132.80, 130.00, 129.76, 129.70, 127.78, 127.69, 127.57, 75.51, 67.01, 51.33, 41.47, 40.06, 26.92, 26.84, 19.28, 19.22.

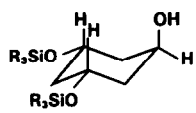
Compound 13: oil; IR ($CHCl_3$): 1735 cm^{-1} (ester and aldehyde CO); ^{1}H NMR ($CDCl_3$): δ 0.98 (s, 9H), 1.02 (s, 9H), 1.90-2.45 (m, 4H), 3.30 (s, 3H), 4.17-4.24 (m, 2H), 7.20-7.75 (m, 20H), 9.48 (t, J=2 Hz, 1H).

7. Deslongchamps, P., Atlani, P., Frehel, D., Malaval, A., Moreau, C., Can. J. Chem., **1974**, 52, 3651.

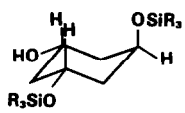
8. In the silylation of cis-cis and cis-trans cyclohexane triols 10 (ratio 1:1), only two (ie., 11a and 11b) of the three possible disilylated products were obtained. This is in



11a



11b



agreement with published observations (Greene, T.W.: Protective Groups in Organic Chemistry, John Wiley & Sons, New York, **1981**, p. 40) that equatorial hydroxy groups silylate faster than axial ones. In the above silylations significant amounts of the corresponding trisilylated products were isolated, however.

9. The ozonolysis mixture obtained from the bicyclic olefin 6 gave a negative perioxide test (EM Quant® strips); on the other hand, the mixture obtained from the ozonolysis of the monocyclic 12 showed an intense blue color in the test. Enhanced stability of the cyclic peracetal (Scheme II) compared to that of the acyclic alkoxy-hydroperoxide (Scheme III) may be the reason for this difference.

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