Oxidation of Cyclopropane Terpenoids with Ruthenium Tetraoxide

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Oxidation products of cyclopropanoid terpenes, (−)-carane (4), (+)-cyclosativene (5), laurinterol methyl ether (6), and thujaopsane (7), with ruthenium tetraoxide were investigated.

Key words absolute configuration; ruthenium tetraoxide; terpene; cyclopropane

Recently, we have reported the isolation of a new sesquiterpene, cyclosativanuline (1) from a soft coral collected off Ishigaki Island. The compound is a tetracyclic hydrocarbon composed of a cyclopropane ring. Its absolute configuration has been undetermined because it is an oily substance and no oxygen function necessary for chemical derivatization is present. If a carbonyl group could be introduced on one of the methylene carbons, the absolute configuration would be determined by means of the modified Mosher’s method (3) after the carbonyl is reduced to a hydroxy group. This seemed feasible because Hasegawa and co-workers reported that ruthenium tetraoxide oxidation of cyclopropyl hydrocarbons afforded α-ketocyclopropanes as exemplified by reaction 2 to 3. Coudret and co-workers also reported the same category of the reactions. (4)

Because of the limited amount of 1, (−)-carane (4), (+)-cyclosativene (5), laurinterol methyl ether (6), and thujaopsane (7) were chosen as substrates, and they were subjected to ruthenium tetraoxide oxidation.

Results and Discussions

The reaction conditions were the same as those reported by Hasegawa and co-workers. (3) The substrate was treated with ruthenium chloride (0.2–0.3 eq) and an excess (3 eq) of sodium periodate in carbon tetrachloride-acetonitrile and a phosphate buffer solution (pH 7). The reaction was carried out at room temperature (rt) for 24–26 h.

Oxidation of (−)-Carane and Application of the Modified Mosher’s Method (−)-Carane (4) was prepared from commercially available (+)-3-carane by borane reduction. The ruthenium oxide oxidation of 4 for 24 h afforded 5-caranone (8) in 75% yield. The ketone was reduced with diisobutylaluminum hydride, and the volatile alcohol (9) was, without purification, converted to (R)- and (S)-methoxy-(phenyl)trifluoromethylacetic acid (MTPA) esters (10, 11) by using 2,4,6-trinitrochlorobenzene as a condensation reagent. (5)

The β-configuration of the oxygen function at C-5 was determined by the nuclear Overhauser effect spectroscopy (NOESY) observed between 5α-H and 3α-H as well as 5α-H and 6α-H observed for 11. The Δδ values [δα-((13)C)/δα-MTPA] were calculated as shown in 12. (6) The absolute configuration predicted on the basis of these values is identical with the known one.

These results indicated that combination of the ruthenium tetroxide oxidation and the modified Mosher’s method would be useful for the absolute configuration determination of cyclopropane terpenoids.

Encouraged by the positive findings, we further advanced toward more complex cyclopropanoids, which turned out to produce unexpected products.

Oxidation of (+)-Cyclosativene Commercially available (+)-cyclosativene (5) afforded three products, 13 (15%), 14 (7%) and 16 (5%), by the ruthenium oxidation.

The major product 13 exhibited a molecular ion at m/z 220.1835 (C13H21O) and it showed a carbon signal at δ 74.5 (s) due to an oxygenated quaternary carbon in its 13C-NMR spectrum. The cyclosativene framework and the position of the hydroxy group were deduced by the extensive study of the two dimensional (2D) NMR spectra including the hetronuclear multiple bond connectivity (HMBC) spectrum. The correlations observed between protons and carbons are illustrated in 13a. The orientation of the hydroxy group was supposed to be α, that is C-5(β), by the cross peaks observed in the nuclear Overhauser effect spectroscopy (NOESY) spectrum [13b], and the α-orientation was further confirmed by the titration study using a paramagnetic shift reagent, Eu(fod)3. (7) The downfield shift of H-1 is greater (Δδ = 0.46) than that of H-7 (Δδ = 0.25) when Eu(fod)3/13 = 0.27 in 54 mm CDCl3 solution of 13.

The second product had an unexpected structure. The molecular formula was established by high resolution (HR)-MS as C14H21ClO, showing that one carbon was eliminated from cyclosativene (5) and a chlorine atom was incorporated, which was verified by appearance of M+ 2 ion at m/z 242 (33% intensity of the molecular ion). The IR absorption at 1748 cm−1 and the 13C signal at δ 216.8 indicated the presence of a cyclopentanone moiety. Two possible structures, 14 and 14′, were deducible for this product even after the 2D NMR (hetronuclear single quantum coherence (HMQC), HMBC, NOESY etc.) studies, because there was an ambiguity in the assignment of two methine signals at δC 57.1/δH 3.68 (br s) and δC 61.4/δH 2.77 (br s). These signals could be assigned as C-7 and C-9 of either 14 or 14′. Therefore, this product was transformed into an alcohol (15) by reduction with sodium borohydride. C-8 of 15 appears at δ 80.6, and by the HSQC spectrum, H-8 (δ 3.81) was assignable. H-8 is coupled with H-9 (δ 2.47) (J = 3.6 Hz) which was further correlated with a methine (δC 4.25/δH 5.65) assignable as H-7. Structure 15 was eventually confirmed by the NOESY spectrum (see 15), and these findings led to the structure of 14 as the oxidation product.

The third oxidation product (C13H22O4 by HR-MS: m/z 267.1597 [M+1] showed two signals of ester carbonyl carbons at δ 167.1 (s) and 168.0 (s). The IR spectrum exhibited a strong absorption band at 1749 cm−1, suggesting the presence of strained ester moieties. In the 13C-NMR spectrum an acetalic carbon shows a signal at δ 110.1 (C-8), to which two
Here we considered the pathway to produce 13, 14, and 16. Inertness of the methylene group at C-10 of cyclotosativene (5) against oxidation may be ascribed to the steric hindrance by the surrounding aliphatic moieties, especially from methyl-11. It has been reported that a hydroxy group is introduced to a tertiary carbon, as in the case of 13, by oxidation with ruthenium tetroxide, which can oxidize a methine rather than a methylene or methyl because the C–H bond of the former is more electron-rich than that of the latter. The oxidation at C-5 took place from the less crowded side to give the α-hydroxy product (13).

Formation of the chloroketone (14) is quite puzzling. The chlorine atom apparently originated from ruthenium chloride. A possible pathway leading to 14 is described in Fig. 1. Although disfavored, the methyl hydrogens can be nevertheless attacked by RuO₄. Then a chloride anion attacks at C-7 carbon with concomitant C7–C8 bond cleavage. Oxidative cleavage of the exomethylene group with ruthenium tetroxide affords 14. It is peculiar, however, that the chlorine atom is introduced from the more hindered side (C-7) rather than from the less crowded direction (C-9).

Peroxidation of the cyclopropane ring of 5, two methines at C-7 and 9 giving carboxyl groups and the quaternary carbon at C-8 transforming to a ketone (16'), produces 16. To our best knowledge, this type of oxidation of 1,1,2,3-tetrasubstituted cyclopropane may be the unprecedented one.

**Oxidation of Laurinterol Methyl Ether** Laurinterol was obtained from the red alga Laurencia intermedia YAMADA. The phenolic hydroxy group was converted into a methyl ether (6) to prevent the oxidation of the phenyl group. Oxidation of 6 under the conditions described above afforded a product (C₁₆H₁₈BrO₂; HR-MS m/z 322.0546) in 32% yield. This compound showed an intense IR absorption band at 1660 cm⁻¹ due to a conjugated enone. Presence of the enone system was further confirmed by the singlets at δ 5.88 (1H) and 1.65 (3H) ascribable to α-proton of the α,β-unsaturated ketone and the olefinic methyl, respectively, in the ¹H-NMR spectrum and by the olefinic carbon signals at δ 169.4 (s) and 125.8 (d) and a carbonyl carbon signal at δ 198.9 in the ¹³C-NMR spectrum. Presence of 5-bromo-2-methoxy-4-methylphenyl group and vicinal two methylene groups were obvious from the NMR properties, and structure 18 was assigned for this oxidation product.

Instead of oxidizing the methylene group (C-5) adjacent to the cyclopropyl moiety, ruthenium tetroxide cleaved, as in the case of 14, one (C₂–C₄) of the cyclopropyl bonds to give possibly the hydroxy ketone (17), which afforded 18 by dehydration.
Oxidation of Thujopsane

We were further interested in the mode of ruthenium tetroxide oxidation of a cyclopropane compound. Thujopsene (7), obtained by reduction of thujopsone with borane, was chosen as another example and subjected to the ruthenium oxidation.

The product turned out to be a ketocarboxylic acid (19) that was isolated as a methyl ester (20) after treatment with diazomethane. It should be remarkable that the same compound (19) was obtained by oxidation of thujopsene under the same conditions. Although the latter type of oxidative cleavage of an olefin is already documented, the capture of the sigma bond adjacent to a cyclopropane ring into a dicarbonyl moiety must be unique.

Coudret and co-workers reported the same type of oxidative cleavage in the ruthenium oxide oxidation of cyclopropane compounds.13 According to the proposed mechanism, a hydroxy group is at first introduced at C-2 as in the case of 13, the tertiary alcohol is dehydrate to thujopsene, and then the oxidative cleavage of the double bond takes place.

Conclusion

Four cyclopropane terpenoids, (−)-carane (4), (+)-cyclosativene (5), laurinterol methyl ether (6), and thujopsane (7) were subjected to ruthenium tetroxide oxidation. (−)-Carane (4) afforded a ketone (8), the reduction product (9) of which was subjected to the modified Mosher’s method to confirm the absolute configuration. In the case of 5 and 6, carbonyl functions were not introduced at the α-methylenes of the cyclopropane rings. (+)-Cyclosativene (5) afforded a tertiary alcohol 13 as well as a chloroketone 14 and an acetal diester 16, which resulted from the oxidative degradation of the cyclopropane ring. The cyclopropane ring of laurinterol methyl ether (6) was labile under the oxidation conditions, and the reaction produced a cyclohexenone (18). The ruthenium oxidation of thujopsane (7) resulted in the unusual cleavage of the sp2−sp3 sigma bond β to the cyclopropane ring to produce a ketocarboxylic acid (19).

The result obtained for (+)-cyclosativene (5) is informative for elucidating the absolute configuration of cyclosativulane (1): Formation of 14 from 5 suggests that a similar chlorine ketone could be produced by ruthenium oxide oxidation of 1. The ketone would be transformed to an alcohol analogous to 15, to which the modified Mosher’s method would be applicable. An attempted experiment along this line is in progress.

Experimental

1H- and 13C-NMR spectra were measured with JEOL AL-400 and Bruker ARX-400 spectrometers. IR spectra were measured on an FT/IR-420 spectrophotometer. Low resolution (LR)-MS spectra were taken on a JEOL JMS-ARX-400 spectrometers. IR spectra were measured on an FT/IR-420 spectrophotometer. Low resolution (LR)-MS spectra were taken on a JEOL JMS-ARX-400 spectrometers. IR spectra were measured on an FT/IR-420 spectrophotometer. Low resolution (LR)-MS spectra were taken on a JEOL JMS-ARX-400 spectrometers. IR spectra were measured on an FT/IR-420 spectrophotometer. Low resolution (LR)-MS spectra were taken on a JEOL JMS-ARX-400 spectrometers. IR spectra were measured on an FT/IR-420 spectrophotometer. Low resolution (LR)-MS spectra were taken on a JEOL JMS-ARX-400 spectrometers. IR spectra were measured on an FT/IR-420 spectrophotometer. Low resolution (LR)-MS spectra were taken on a JEOL JMS-ARX-400 spectrometers. IR spectra were measured on an FT/IR-420 spectrophotometer. Low resolution (LR)-MS spectra were taken on a JEOL JMS-ARX-400 spectrometers. IR spectra were measured on an FT/IR-420 spectrophotometer. Low resolution (LR)-MS spectra were taken on a JEOL JMS-ARX-400 spectrometers. IR spectra were measured on an FT/IR-420 spectrophotometer. Low resolution (LR)-MS spectra were taken on a JEOL JMS-ARX-400 spectrometers. IR spectra were measured on an FT/IR-420 spectrophotometer. Low resolution (LR)-MS spectra were taken on a JEOL JMS-ARX-400 spectrometers. IR spectra were measured on an FT/IR-420 spectrophotometer. Low resolution (LR)-MS spectra were taken on a JEOL JMS-ARX-400 spectrometers. IR spectra were measured on an FT/IR-420 spectrophotometer. Low resolution (LR)-MS spectra were taken on a JEOL JMS-ARX-400 spectrometers. IR spectra were measured on an FT/IR-420 spectrophotometer. Low resolution (LR)-MS spectra were taken on a JEOL JMS-ARX-400 spectrometers. IR spectra were measured on an FT/IR-420 spectrophotometer. Low resolution (LR)-MS spectra were taken on a JEOL JMS-ARX-400 spectrometers. IR spectra were measured on an FT/IR-420 spectrophotometer. Low resolution (LR)-MS spectra were taken on a JEOL JMS-ARX-400 spectrometers. IR spectra were measured on an FT/IR-420 spectrophotometer. Low resolution (LR)-MS spectra were taken on a JEOL JMS-ARX-400 spectrometers. IR spectra were measured on an FT/IR-420 spectrophotometer. Low resolution (LR)-MS spectra were taken on a JEOL JMS-ARX-400 spectrometers. IR spectra were measured on an FT/IR-420 spectrophotometer. Low resolution (LR)-MS spectra were taken on a JEOL JMS-ARX-400 spectrometers. IR spectra were measured on an FT/IR-420 spectrophotometer. Low resolution (LR)-MS spectra were taken on a JEOL JMS-ARX-400 spectrometers. IR spectra were measured on an FT/IR-420 spectrophotometer. Low resolution (LR)-MS spectra were taken on a JEOL JMS-ARX-400 spectrometers. IR spectra were measured on an FT/IR-420 spectrophotometer. Low resolution (LR)-MS spectra were taken on a JEOL JMS-ARX-400 spectrometers. IR spectra were measured on an FT/IR-420 spectrophotometer. Low resolution (LR)-MS spectra were taken on a JEOL JMS-ARX-400 spectrometers. IR spectra were measured on an FT/IR-420 spectrophotometer. Low resolution (LR)-MS spectra were taken on a JEOL JMS-ARX-400 spectrometers. IR spectra were measured on an FT/IR-420 spectrophotometer. Low resolution (LR)-MS spectra were taken on a JEOL JMS-ARX-400 spectrometers. IR spectra were measured on an FT/IR-420 spectrophotometer. Low resolution (LR)-MS spectra were taken on a JEOL JMS-ARX-400 spectrometers. IR spectra were measured on an FT/IR-420 spectrophotometer. Low resolution (LR)-MS spectra were taken on a JEOL JMS-ARX-400 spectrometers. IR spectra were measured on an FT/IR-420 spectrophotometer. Low resolution (LR)-MS spectra were taken on a JEOL JMS-ARX-400 spectrometers. IR spectra were measured on an FT/IR-420 spectrophotometer. Low resolution (LR)-MS spectra were taken on a JEOL JMS-ARX-400 spectrometers. IR spectra were measured on an FT/IR-420 spec...
Preparation of Thujopsane (7) To a solution of thujopsane (2.4 g, 11.7 mmol) in dry THF (7 ml) was added dimethyl sulfoxide borane complex (2.3 ml, 24.2 mmol) at 0°C under argon. After the mixture was stirred for 15 h at rt, water was added to the reaction mixture, and the solution was extracted with dichloromethane (3 x). The organic layer was washed with brine, dried over anhydrous Na2SO4 and concentrated to give a residue (yellow oil, 1.7 g), which was chromatographed on silica gel to afford 7 (137mg, 6% yield) as colorless oil.

[7-H-NMR (400 MHz, CDC13): δ: 0.012 (1H, t, J = 5.2 Hz, 1H), 0.39 (1H, dd, J = 10.0, 5.2 Hz, 1H) 0.51 (3H, s, 8-CH3), 0.88 (1H, dd, J = 10.0, 5.6 Hz, 1H). (0.1H, m, 7-CH3), 1.03 (1H, m, 6-CH3), 1.17 (1H, s, 6-CH3), 1.17 (1H, d, J = 13.4, 4.8 Hz), 1.19 (1H, m, 5-CH3), 1.47 (1H, sept., J = 6.6, 2.2 Hz, 1H), 1.60 (1H, br, d, J = 13.4 Hz, 4.8 Hz), 1.88 (1H, d, J = 6.6 Hz, 13.4 Hz), 2.05 (1H, dd, J = 11.0, 3.0 Hz, 10-CH2), 2.35 (3H, s, 2-CH3), 2.76 (1H, br, d, 6-H), 2.76 (1H, brs, 9-H), 3.50 (1H, brs, 7-H).

13C-NMR (100 MHz, CDCl3): δ: 20.7 (C-13), 21.1 (C-14), 22.1 (C-15), 23.0 (C-16), 30.7 (C-12), 32.6 (C-10), 33.9 (C-9), 44.1 (C-6), 46.2 (C-1), 50.2 (C-15), 56.7 (C-7), 61.2 (C-9), 219.5 (C-8).

Preparation of Lauritinal Methyl Ether (6) A solution of laurtinol (300 mg, 1.0 mmol) in dry THF (10 ml) was treated with sodium hydride (60% dispersion in mineral oil, 79.9 mg, 2.0 mmol) under nitrogen. The mixture was stirred at rt for 30 min. Then, iodomethane (0.30 ml, 5.0 mmol) was added to the mixture. After the mixture was stirred for 10 h at rt, water and ether were added and the organic layer was washed with 1N NaOH, water and brine. The organic layer was dried over anhydrous Na2SO4 and concentrated to give a residue (292 mg) which was chromatographed on silica gel to afford 6 (229 mg, 74%) as white crystals.

[6-H-NMR (400 MHz, CDCl3): δ: 0.47—0.52 (2H, m, overlap), 1.06 (1H, t, J = 7.6, 4.0 Hz), 1.17 (1H, td, J = 12.2, 8.2 Hz), 1.29 (3H, s), 1.35 (3H, s), 1.60 (1H, dd, J = 12.0, 8.0 Hz), 1.91 (1H, m, 1-H), 2.16 (1H, dd, J = 13.4, 5.8 Hz), 2.35 (3H, s, benzylic-CH3), 2.76 (3H, s, -OCH3), 6.72 (1H, s, Ph-H), 7.67 (1H, s, Ph-H).

Oxidation of Lauritinal Methyl Ether (6) Lauritinal methyl ether (16.9 mg, 0.063 mmol) was oxidized for 26 h. After the crude product was purified by preparative TLC, 18 (6.5 mg, 0.020 mmol, 32%) was obtained.

[18-H-NMR (400 MHz, CDCl3): δ: 1.59 (3H, s, CH3), 1.65 (3H, s, CH3) (J = 7.6 Hz, allylic-CH, 1.69 (1H, tt, J = 6.4, 4.0 Hz), 2.35 (1H, tt, J = 16.8, 4.8 Hz), 2.37 (3H, s, benzylic-CH3), 2.53 (1H, dd, J = 17.4, 12.8, 5.2 Hz, 2.71 (1H, d, J = 12.8, 4.8 Hz), 3.72 (3H, s, -OCH3), 5.88 (1H, s, olefin-CH, 6.72 (1H, s, Ph-H), 7.34 (1H, s, Ph-H).

13C-NMR (100 MHz, CDCl3): δ: 20.9 (q), 22.7 (q), 23.3 (q), 34.6 (t), 35.0 (t), 42.5 (s), 55.0 (q), 113.7 (dl), 115.4 (s), 125.8 (d), 131.1 (d), 133.1 (s), 137.6 (s), 156.3 (s), 169.4 (s), 198.9 (s).

MS m/z (rel. int %): 324 (M+2, 99.8), 322 (100). HR-MS (El) m/z: 322.0546 (Calcd for C18H17BrO2: 322.0568). IR (liquid film) 1660 cm⁻¹.

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