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Terpenoids. XLII.[1] A Convenient Stereoselective Transformation of 16-Exocyclic Methylene Group into Carboxy Group in *ent*-Kaurene and Its 19-Oic Acid

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By the two successive oxidative rearrangements using thallium trinitrate, *ent*-16-kaurene (**1**) was stereoselectively converted into *ent*-16α-kauran-17-oic acid (**30**). Further application of these reactions led to a convenient transformation of *ent*-16-kauren-19-oic acid (**31**) into *ent*-16α-kaurane-17,19-dioic acid (**32**).

Keywords——diterpenoids; thallium trinitrate; oxidative rearrangement; ring expansion; ring contraction; *ent*-16α-kauran-17-oic acid; *ent*-16α-kaurane-17,19-dioic acid

Abley, *et al.*[3] have obtained cyclohexanone, the ring-expanded ketone, in good yield by treatment of methylenecyclopentane with thallium (III) perchlorate in aqueous solution. Farcasiu, *et al.*[4] have reported the formation of bicyclo[3.2.1]octan-2-one from 2-methylenenorbornane by its oxidation with thallium (III) salt.

Thallium (III) salts also react on carbonyl compounds to give products derived from α-hydroxylation or oxidative rearrangement. Their reaction with cyclobutanone or cyclohexanone gives cyclopropane carboxylic acid[5] or cyclopentane carboxylic acid,[6,7] respectively, by ring contraction.

Now, we tried the transformation of exocyclic methylene group into carboxylic acid by a combination of the foregoing reactions of two type (ring expansion and ring contraction), that is, by two successive oxidative rearrangements with thalliun (III) salt.

As described in the preceding reports,[1,8] we have obtained allylic nitrates (**4** and **5** or **6** and **7**) in the reaction of *ent*-16-kaurene (**1**) or 13β-kaur-16-ene (**2**) with thallium trinitrate (TTN) in 1,2-dimethoxyethane (glyme) but not the ring-expanded ketones (*e. g.* **3**). Now, we carried out the reaction of **1** with TTN in methanol which stabilizes ions much more largely than glyme. Consequently, allylic nitrates, **4** and **5**, were scarcely obtained (total yield: 0.4%), but a saturated ketone was yielded as the major product (32.9%). The molecular formula, $C_{20}H_{32}O$, and the infrared (IR) absorption at 1693 cm^{-1} suggested it to be the desired ring-D-expanded homoketone (**3**). The compound on refluxing with sodium in a mixture of deuterium oxide and [^{2}H]methanol gave a mixture of deuterized products, whose mass spectrum (MS) indicated it to consist of d_3 (89%), d_2 (8.3%), d_1 (1.8%), and d_0 (1.7%). Since bicyclo [3.3.1]nonan-2-one on deuterization has given d_3 compound almost entirely,[9] the foregoing observation supported the structure **3a**. Further evidence that the signals at 44.85 ppm assignable to the tertiary carbon atom (methine) and at 38.63 ppm assignable to the secondary carbon atom (methylene) on the basis of the off-resonance

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[1] Part XLI: E. Fujita and M. Ochiai, *J.C.S. Perkin I*, "in press."
[2] Location: *Uji, Kyoto, 611, Japan.*
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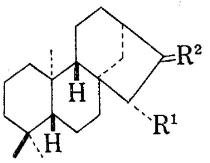
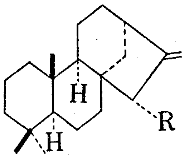
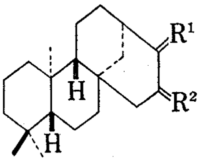
decoupled ^{13}C nuclear magnetic resonance (NMR) spectrum of **3** disappeared in the spectrum of the deuterized sample confirmed the structure and an alternative isomeric structure **3b** was denied. Except for the foregoing products (**3a**, **4**, and **5**), other four products were isolated. Two of them were allylic alcohols (3.2% each), one of which was shown to be identical with the authentic sample of **8**.[1] Another one was isolated as acetate, which was proved to be identical with compound (**10**).[10] The remaining two were allyl methyl ethers, one of which was shown to be the known compound **11**.[1,8] The other one was determined to be *ent*-15β-methoxy-16-kaurene (**12**) by its NMR data: two vinyl protons (δ 5.07 and 5.13), methyl protons of a methoxy group (δ 3.42), and a proton on the methoxylated carbon atom (δ 3.33).



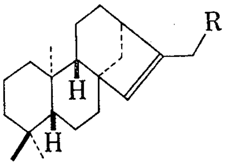
1: R^1=H; R^2=CH$_2$
4: R^1=ONO$_2$; R^2=CH$_2$
8: R^1=OH; R^2=CH$_2$
12: R^1=OCH$_3$; R^2=CH$_2$
30: R^1=H; R^2=α-COOH, β-H



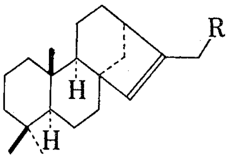
2: R=H
6: R=ONO$_2$
23: R=OH



3a: R^1=O; R^2=H$_2$
3b: R^1=H$_2$; R^2=O



5: R=ONO$_2$
9: R=OH
10: R=OAc
11: R=OCH$_3$



7: R=ONO$_2$
21: R=OH

The pathways of the reaction are shown in Chart 1. Organothallium compound (**15**) which may be produced, from the π complex **13** initially derived from *ent*-16-kaurene (**1**), *via* a concerted process or a carbonium ion **14** can be easily ionized to the allyl cation **16** in methanol. This cation is subject to attack of water of crystallization in TTN or methanol to give products, **8**, **9**, **11** and **12** but nitrates, **4** and **5**, the major products in the reaction in glyme, are only scarcely obtained. The nucleophilic attack of the solvent or water to carbonium ion **14** from the α-side of the ring-D may produce an intermediate **17**, whose heterolysis between C, Tl-bond would bring about rearrangement to the ring-expanded ketone **3a**. As mentioned above, the isomer **3b** is not obtained. The comparison between the transition states **18** and **19** to **3a** and **3b**, respectively, would give a resoanable explanation: **18** has a chair-like conformation and more favored than **19** which has a boat-like conformation. Generally, it has been known that the preferred conformation of bicyclo[3.3.1]nonane is the chair-chair conformation.[11] Thus, the chair-like conformation **18** predominates in the transition state.

No examples for the oxidation of alcohols with thallium (III) salts have been known, but allylic alcohols **8** and **9** may react with the remaining TTN in the reaction medium, and hence their relative formation raio (*ca.* 1:1) is not necessarily the same as the real one. TTN oxidizes some primary allylic alcohols to $\alpha\beta$-unsaturated aldehydes in good yields. For

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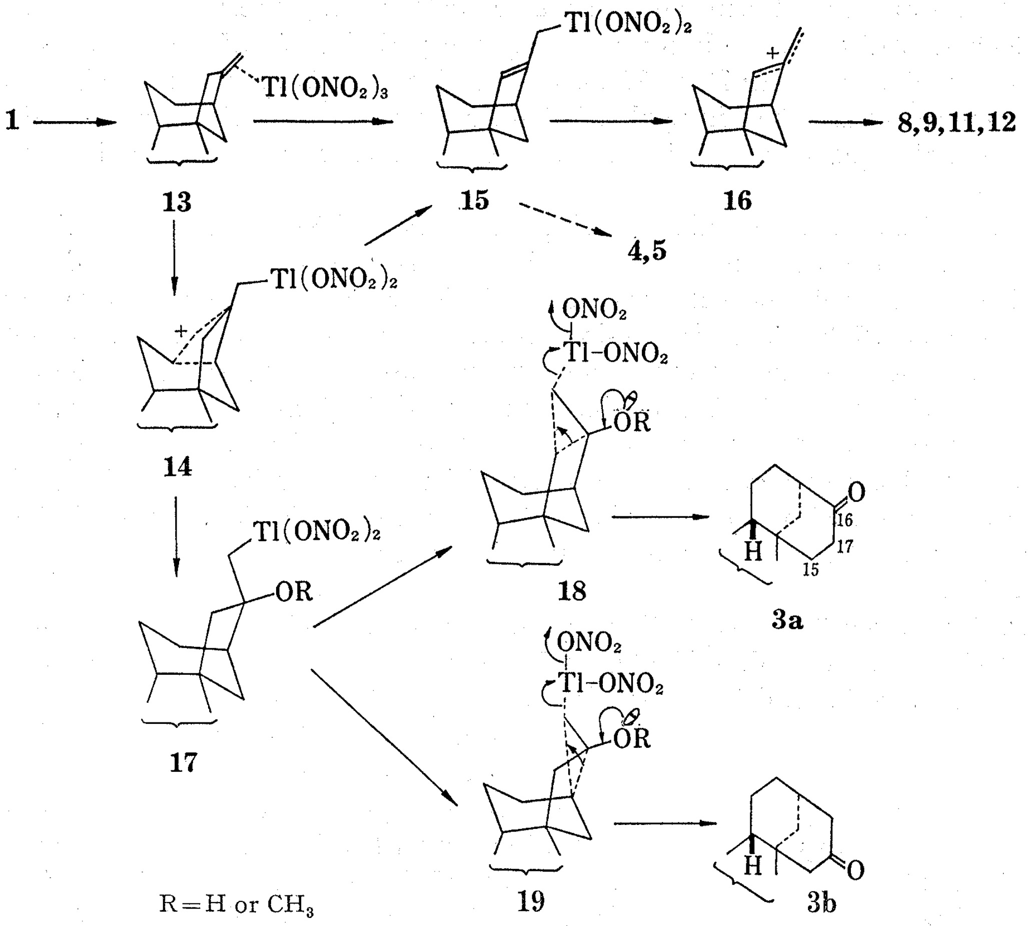


Chart 1

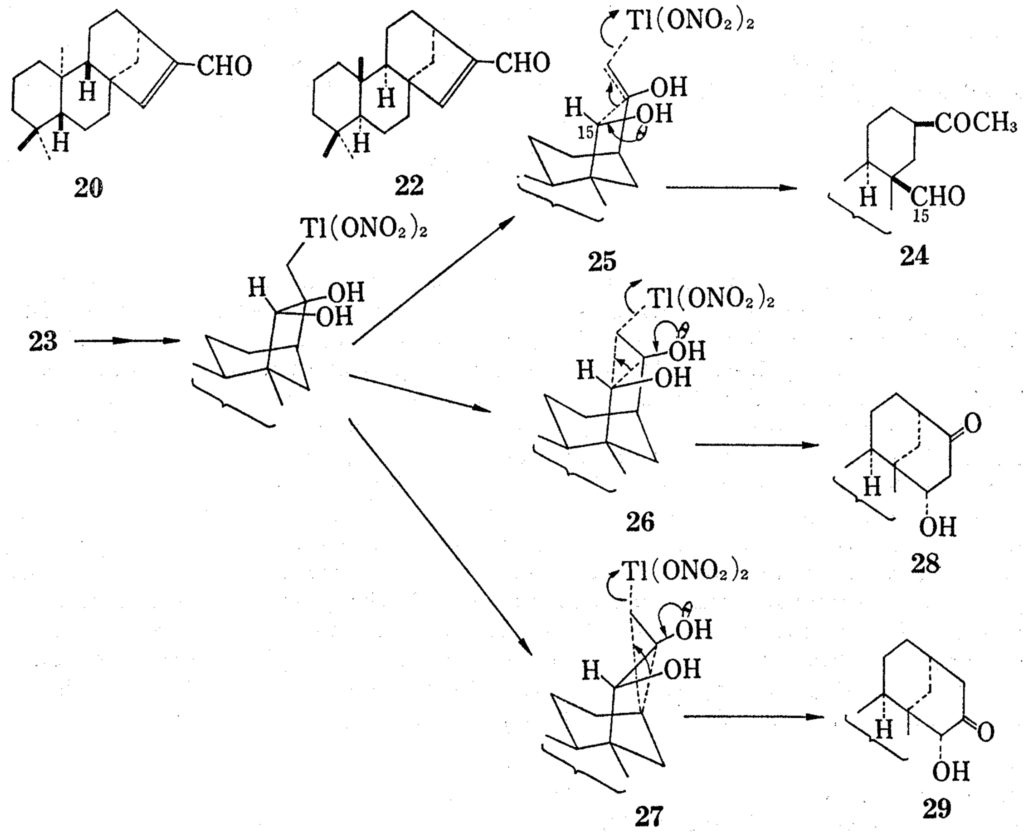


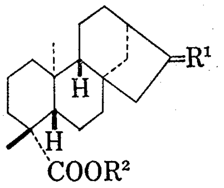
Chart 2

instance, **9** and **21** on treatment with TTN give **20**[1,8] and **22**,[12] respectively, while **23** gives a keto-aldehyde **24**.[13] In the latter case, only the pathway *via* **25** among three potential pathways including those *via* **26** or **27** makes the **15**-carbon atom changable from *sp*^{3} to *sp*^{2} configuration to release the big nonbonded interaction between 15β-H and 20-Me. Thus, the clevage of the ring D into **24** is more favored than the ring expansions into **28** and **29**. (See Chart 2)

The second step *i.e.* the oxidative ring contraction of **3a** was then investigated. The compound **3a** on treatment with TTN for 10 hr in acetic acid gave good yield of a carboxylic acid, which did not coincide with *ent*-kauran-17-oic acid,[14] but was shown to be identical with its 16-epimer **30**.[15] Thus the desired α-carboxylic acid was obtained stereoselectively. The stereochemistry of the carboxy group can be reasonably explained by the mechanism suggested by Wiberg, *et al.*[6] The initial formation of the 17α-thallium adduct, the nucleophilic addition of water to the carbonyl group at C-16, and subsequent rearrangement of 13, 16-bond anti-coplanar to 17α, Tl-bond into 17-position under elimination of the leaving group (Tl substituent) resulted in the formation of 16α-carboxylic acid (**30**). It would be difficult, however, to rationalize this stereochemistry by means of the mechanism suggested by Mckillop, *et al.*[7]

Thus, the two successive oxidative rearrangements led to transformation of *ent*-16-kaurene (**1**) into *ent*-16α-kauran-17-oic acid (**30**), and the 16- and 17-carbon atoms in compound **1** were changed to the 17- and 16-carbons in the product (**30**), respectively.

Subsequently, *ent*-16-kauren-19-oic acid (**31**) was treated with TTN in 95% methanol, and the crude product obtained, dissolved in acetic acid, was allowed again to react with TTN followed by diazomethane to afford dimethyl *ent*-16α-kaurane-17, 19-dioate (**33**)[15] in 32% yield. The direct isolation of *ent*-16α-kaurane-17,19-dioic acid (**32**) without methylation was achieved in 25% yield. The latter has been isolated from *Ricinocarpus stylosus* by Jefferies, *et al.*[15] The interconversion between two natural products *i.e.* **31**→**32** was thus accomplished through the relatively simple and unique pathway.



31: $R^1=CH_2$; $R^2=H$
32: $R^1=\alpha$-COOH, β-H; $R^2=H$
33: $R^1=\alpha$-$COOCH_3$, β-H; $R^2=CH_3$

Experimental

Melting points were taken on a micro hot-stage and uncorrected. IR spectra were recorded with a Hitachi model EPI-S2 spectrometer, NMR spectra with a Varian T-60 spectrometer, and ^{13}C-NMR with a JEOL JMN-FX100 instrument in $CDCl_3$; signals are reported in ppm from TMS as internal standard. MS were taken on a JEOL model JMS-0ISG double-focusing mass spectrometer. Optical rotations were measured on a JASCO DIP-180 automatic polarimeter. Extracts were dried over anhydrous Na_2SO_4. Mallinckrodt silicic acid and Kieselgel 0.05—0.2 mm (Merck) were used for column chromatography. Thin-layer chromatography (TLC) plates were coated with Silica gel G nach Stahl (Merck).

Reaction of *ent*-16-Kaurene (1) with TTN——To a solution of *ent*-16-kaurene (**1**) (1 g) in methanol (100 ml) was added TTN (1.634 g). The mixture was stirred for 30 min at room temperature, precipitating white solid. The solid was filtered off, and the filtrate was concentrated to one tenth in volume. Extraction with ethyl acetate, washing with water, drying, and evaporation *in vacuo* left a crystalline residue, which was chromatographed. Elution with hexane yielded the material **1** (79 mg) and with hexane–methylene chloride (98: 2) a mixture of allylic nitrates, **4** and **5** (5 mg, 0.4%). The ratio of those was determined to be 1: 1 by the NMR analysis. Elution with hexane–methylene chloride (1: 1) yielded two products: the product with larger *Rf* value, *ent*-15β-methoxy-16-kaurene (**12**) (150 mg, 13.5%) was obtained as needles, mp 84—85° (from methanol–acetone). *Anal.* Calcd. for $C_{21}H_{34}O$: C, 83.38; H, 11.33; M, 302.261. Found: C, 82.99;

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H, 11.09; M$^+$, 302.259. IR ν_{max} (KBr): 1655, 903, and 835 cm^{-1}. NMR δ: 0.83, 0.87, 1.03 (each 3H, s), 3.33 (1H, s, 15-H), 3.42 (3H, s, 15-OMe), 5.07, and 5.13 (each 1H, s, 17-H_2). MS *m/e*: 302 (M$^+$), 287 (M$^+$$-CH_3$), 270 (M$^+$$-CH_3OH$), and 255 [M$^+$$-(CH_3OH+CH_3)$]. The product with smaller *Rf* value, *ent*-17-methoxy-15-kaurene (**11**) (306 mg, 27.6%) was obtained as needles, mp 55—56° (from methanol), identical (IR, NMR, and m.mp) with the authentic sample of **11**.[1,8] Elution with hexane–methylene chloride (1: 3) separated needles, mp 92—93° (from methanol), of *ent*-16-kauren-15β-ol (**8**) (34 mg, 3.2%), identical (IR, NMR, and m. mp) with the authentic sample of **8**[1] and plates of ring D-homoketone (**3a**) (289 mg), mp 159—160° (accompanied by sublimation at 140°) (from acetone), $[\alpha]_D^{25}$ $-112°$ (c=1.32, $CHCl_3$). *Anal.* Calcd. for $C_{20}H_{32}O$: C, 83.27; H, 11.18; M, 288.245. Found: C, 83.19; H, 11.42; M$^+$, 288.242. IR ν_{max} ($CHCl_3$): 1693 cm^{-1}. NMR δ: 0.87 (6H, s) and 1.05 (3H, s). Further elution yielded a mixture of **3a** and **9**, from which **3a** (59 mg) (total 32.9%) and **10**[10] (38 mg, 3.1%) were separated after the acetylation of the mixture.

Deuterization of Ketone 3a——To a solution of Na (71 mg) in a mixture of MeOD (4 ml) and D_2O (2 ml) was added ketone **3a** (71 mg) dissolved in dioxane (2 ml), and the mixture was refluxed for 5 hr. After cooling, a white crystalline precipitate separated by the addition of D_2O (2 ml) was collected by filtration and washed with water. Recrystallization from acetone gave plates (66 mg), mp 153—155°. IR ν_{max} (nujol): 2170 and 1703 cm^{-1}. The NMR signals at δ 2.3—2.8 of **3a** disappeared in this substance and MS showed this substance to be a mixture of d_0-(1.7%), d_1-(1.8%), d_2-(8.3%), and d_3-(89%) substituted derivatives.

Oxidation of Allylic Alcohol 9 with TTN——To a solution of allylic alcohol **9** (209 mg) in 1,2-dimethoxyethane (10 ml) was added TTN (387 mg). After stirring for 20 min at room temperature, the same treatment as in **1** left a crystalline mass. Recrystallization from ethanol yielded α,β-unsaturated aldehyde **20** (155 mg, 75%) as plates, mp 116—118°, identical (IR, NMR, and m.mp) with the authentic sample of **20**.[1]

Oxidation of Allylic Alcohol 21 with TTN——Oxidation of **21** (4 mg) with TTN (9 mg) was carried out as above to give α,β-unsaturated aldehyde **22** (3 mg, 76%) as plates (from aqueous ethanol), mp 126—128° (*lit.*[12] 129—130°). IR ν_{max} ($CHCl_3$): 1664 and 1594 cm^{-1}. NMR δ: 0.75, 0.83, 0.88 (each 3H, s), 6.85 (1H, s, 15-H), and 9.72 (1H, s, 17-H).

Oxidation of Allylic Alcohol 23 with TTN——Oxidation of **23** (23 mg) with TTN (53 mg) was carried out as above. After stirring for 2.5 hr at room temperature, the same treatment as in **1** left an oil, which was chromatographed to yield keto aldehyde **24** (11 mg, 45%) as plates (from methanol), mp 136—138° (*lit.*[13] 138—140°). IR ν_{max} ($CHCl_3$): 1703 cm^{-1}. NMR δ: 0.77 (6H, s), 0.85 (3H, s), 2.08 (3H, s, $-COC\underline{H}_3$), and 9.85 (1H, s, $-C\underline{H}O$). MS *m/e*: 304 (M$^+$), 289 (M$^+$$-CH_3$), 276 (M$^+$$-CO$), and 261 (M$^+$$-CH_3CO$).

Reaction of 3a with TTN——TTN (59 mg) was added to a solution of **3a** (32 mg) in acetic acid (2 ml). The mixture was stirred vigorously for 10 hr at room temperature, precipitating white thallium (I) nitrate gradually. The inorganic salt was filtered off, and the filtrate was extracted with ether. After washing with sodium carbonate and water and drying, the solvent was evaporated off to leave an oil, which was purified by chromatography to give *ent*-16α-kauran-17-oic acid (**30**) (29 mg, 86%) as needles, mp 217—218° (from acetone), $[\alpha]_D^{20}$ $-69.9°$ (c=0.12, $CHCl_3$), identical (TLC, IR, NMR and m.mp) with the authentic sample of **30**.[15]

Dimethyl *ent*-16α-Kaurane-17,19-dioate (**33**)——*ent*-16-Kauren-19-oic acid (**31**) (60 mg) in methanol (6 ml) and water (0.3 ml) was oxidized with TTN (106 mg) as above. The crude product obtained from the methylene chloride extract weighed 69 mg. To its solution in acetic acid (4 ml) was added TTN (106 mg), and the mixture was stirred for 12 hr at room temperature. After removal of inorganic salt by filtration, evaporation of the filtrate *in vacuo* left a residue (74 mg), to whose solution in methanol (2 ml) was added a solution of excess diazomethane in ether. Evaporation left an oil, which was chromatographed to give dimethyl *ent*-16α-kaurane-17,19-dioate (**33**) (23 mg, 32%) as needles (from aqueous methanol), mp 108—109° (*lit.*[15] 108—109°). *Anal.* Calcd. for $C_{22}H_{34}O_4$: M, 362.246. Found: M$^+$, 362.244. NMR δ: 0.80, 1.17 (each 3H, s), and 3.67 (6H, s). MS *m/e*: 362 (M$^+$), 330 (M$^+$$-CH_3OH$), 303 (M$^+$$-COOCH_3$), and 302 (M$^+$$-HCOOCH_3$).

***ent*-16α-Kaurane-17,19-dioic Acid** (**32**)——*ent*-16-Kauren-19-oic acid (**31**) (220 mg) was oxidized with TTN in methanol–water and then with TTN in acetic acid as above. Chromatography gave *ent*-16α-kaurane-17,19- dioic acid (**32**) (62 mg, 25%) as needles (from methanol), mp 270—272°, identical (TLC, IR, and m.mp) with the authentic sample of **32**.[15]

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