The chemistry of thujone. XIX.[1] Acid-promoted ring cleavage of thujone-derived cyclopropylcarbinols

James P. Kutney, Yong-Huang Chen, and Steven J. Rettig

Abstract: Thujone-derived cyclopropylcarbinols can cleave via three distinct pathways: the *exo* cleavage, the *endo* cleavage, and the interesting cyclopropylcarbinyl rearrangement. Factors determining which pathway is adopted under specific conditions are discussed. A short sequence leading to synthesis of the sesquiterpene (+)-β-cyperone is described.

Key words: thujone, cyclopropylcarbinols, cyclopropylcarbinyl rearrangement, β-cyperone synthesis.

Résumé : Les cyclopropylcarbinols dérivés de la thujone peuvent subir trois clivages distincts : le clivage *exo*, le clivage *endo* et l'intéressant réarrangement cyclopropylcarbinyle. On discute des facteurs qui déterminent le processus suivi dans des conditions spécifiques. On décrit une courte séquence conduisant à la synthèse du sesquiterpène (+)-β-cypérone.

Mots clés : thujone, cyclopropylcarbinols, cyclopropylcarbinyle, réarrangement, synthèse de la β-cypérone.

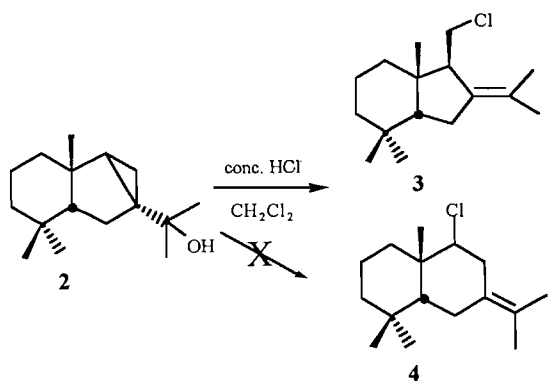
[Traduit par la rédaction]

In continuing the development of the monoterpene thujone (**1**)[3] as an efficient chiral building block (1), we discovered a novel procedure for functionalizing thujone and its derivatives of general structure (i) by ozonation (Fig. 1) (2). The ozonation procedure provides two valuable intermediates of general structures (ii) and (iii) amenable for synthetic exploitation. The cyclopropylcarbinols have been applied in the synthesis of antifeedant polygodial derivatives (2) and the fragrance compounds damascone and damascenone (2, 3). The cyclopropyl ketone derivatives, on the other hand, have been utilized in the synthesis of ambergris fragrances (2). In this article, we would like to detail our recent studies on acid-promoted ring cleavage of thujone-derived cyclopropylcarbinols.

Cleavage reactions, *exo* and *endo*

It is well known that cyclopropylcarbinols can be readily cleaved in the presence of acids (4). Thujone-derived nonsymmetrically substituted cyclopropylcarbinols of structure (ii) in Fig. 1 are expected to produce two regioisomers. For example, the nucleophilic attack of halide X^- at C5 in (ii) will lead to a homoallylic halide of a cyclohexyl skeleton, through cleavage of the C5—C1 bond (i.e., *endo* cleavage); the nucleophilic attack of halide X^- at C6 will form a homoallylic halide of a cyclopentyl skeleton, through cleavage of the C6—C1 bond (i.e., *exo* cleavage) (Fig. 2).

When the thujone-derived alcohol **2** was treated with concentrated hydrochloric acid in methylene chloride, homoallylic chloride **3** was obtained in 85% yield by the *exo*-cleavage pathway. The putative *endo*-cleavage product **4** was not isolated. In brief, the ^{1}H NMR spectrum of **3** showed two methyl singlets at δ 1.63 and 1.70 ppm, indicating the presence of an isopropylidene group, and a multiplet (2H, octet) at δ 3.55 ppm, characteristic of the A/B portion of an ABX system, corresponding to the chloromethylene group.



2 **3** **4**

Treatment of another thujone-derived cyclopropylcarbinol **5** with concentrated HCl also gave the *exo*-cleavage product **6** as the major product (75% yield), the *endo*-cleavage product was not isolated.

Stirring of chloride **6** in the presence of silica gel in methylene chloride overnight regenerated the starting ketol **5** exclusively. The β orientation of the chloromethyl group of the *exo*-cleavage products was therefore verified.

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[3] This natural product is actually a mixture of two epimers, (−)-α-thujone (α-methyl at C-4) and (+)-β-thujone (β-methyl at C-4) in a ratio of 10:1, respectively. However, any base-catalyzed condensation at C-4 leads to only one chiral isomer with the angular methyl group in a β orientation as shown in partial structure (i) (Fig. 1).

Fig. 1.

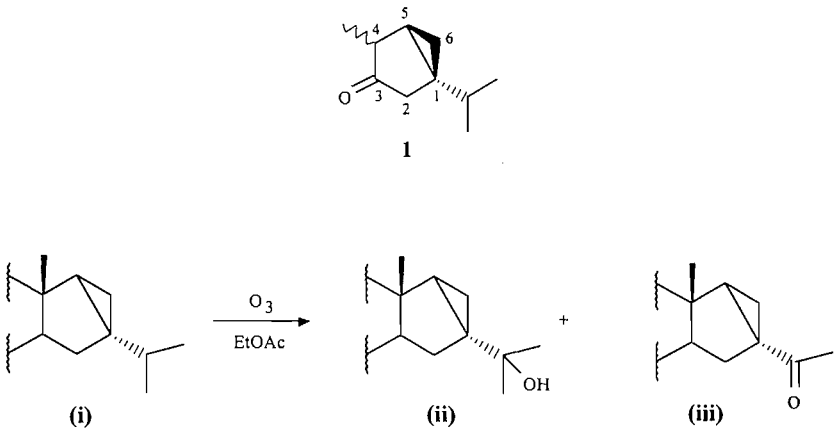
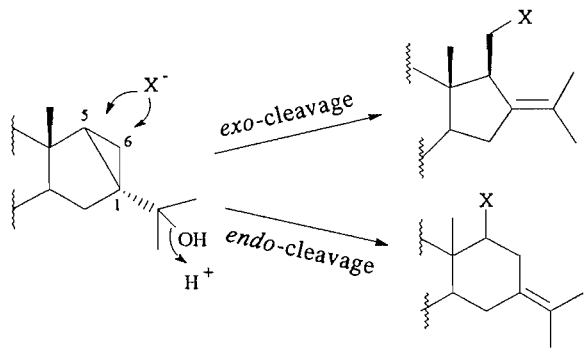


Fig. 2.



The hydrochloric acid promoted *exo*-cleavage reaction is applicable to other thujone-derived cyclopropylcarbinols with a saturated sp^3-hybridized C3 centre. For example, compound **7** was converted to chloride **8** in the synthesis of drimane antifeedant analogues (2). In a sequence leading to synthesis of the rose oil fragrances, β-damascone and β-damascenone (2, 3), thujone derivative **9** was converted into **10**.

It appears that the nucleophilic attack of chloride is concurrent with the cleavage of the C—C bond. Otherwise, if the C—C bond cleavage preceded the chloride attack, the *endo*-cleavage pathway would generate a more stable secondary carbocation as its intermediate and might become the dominant pathway. This conclusion is consistent with the previous observation with regard to the stereochemistry of the acid-promoted cleavage of 1-alkoxymethyl bicyclo[3.1.0]hexanes (5). Therefore, the preference for this *exo* cleavage is very likely due to the more exposed and accessible nature of the C6 methylene compared to the C5 methine in the cyclopropyl ring.

However, the regioselectivity of ring cleavage is altered under the same experimental conditions, when thujone-derived cyclopropylcarbinols are sp^2-hybridized at C3. Thujonol (**11**), which is a mixture of C4 epimers (**11**α and **11**β in a ratio of 10:1), was treated with concentrated hydrochloric acid at room temperature to give carvacrol (**12**) (6) and the chloro-enone **13** in 40 and 45% yields, respectively.

The chloro-enone **13** was rather unstable and therefore the ^1H NMR spectrum obtained was always contaminated with extra signals due to the presence of carvacrol (**12**). However, a "difference spectrum" between the "contaminated spectrum"and the spectrum of **12** clearly revealed all signals of **13**.

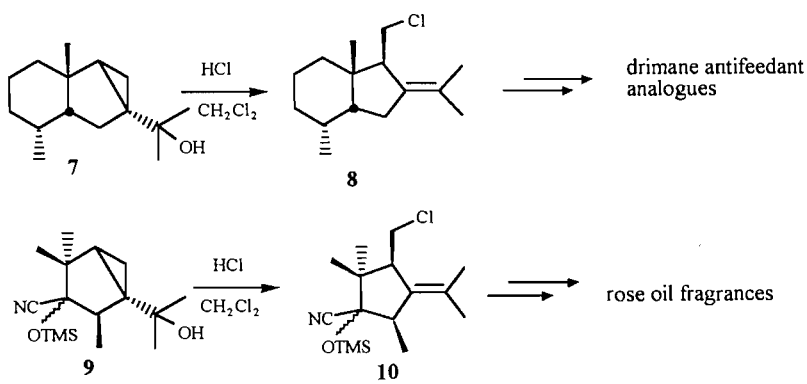


Fig. 3. A formal synthesis of (+)-β-cyperone (**17**).

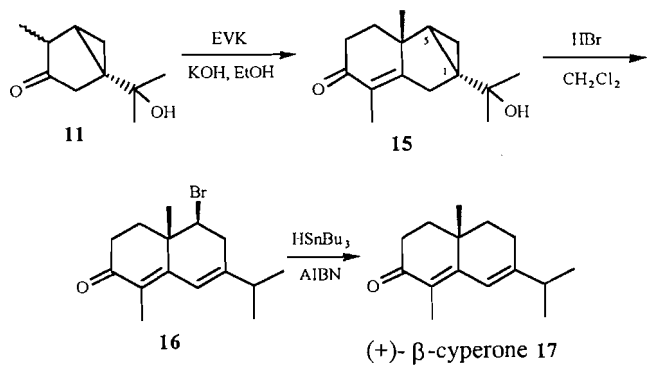
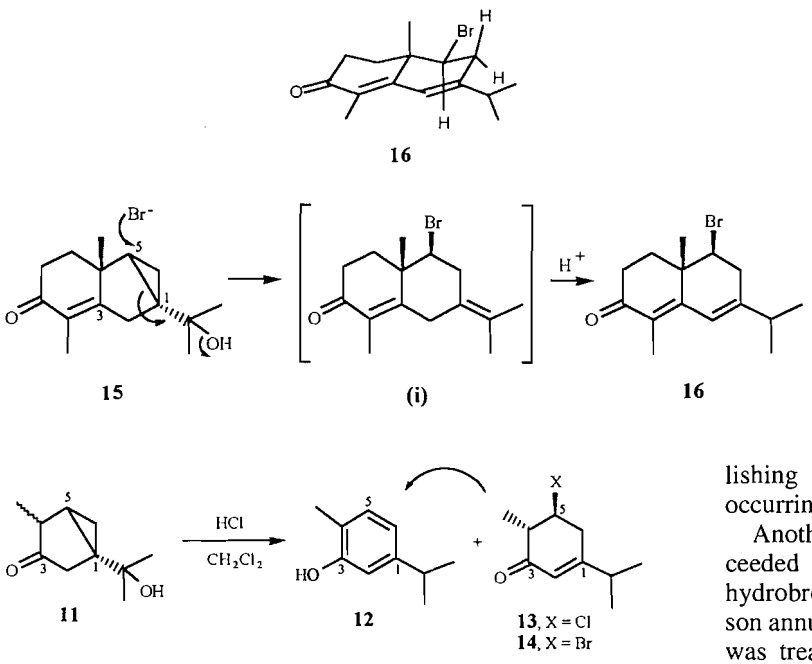


Fig. 4. The ring cleavage reaction of **15** via the *endo*-type cleavage pathway.



This difference spectrum of **13** showed a multiplet (doublet of triplet) at δ 4.06 ppm (1H, J = 4.4 and 9.8 Hz) corresponding to the methine proton at the chlorine bearing carbon (C5), and a broad singlet at δ 5.95 ppm (1H) due to the olefinic proton at C2. The splitting pattern of the methine at C5 indicated that the methyl group and the chlorine are in the *trans* configuration. The nucleophilic attack of the chloride anion from the back side of the cleaving C1—C5 bond should afford the designated β orientation of the chlorine as shown in **13**.

Thujonol (**11**) was also treated with concentrated hydrobromic acid in methylene chloride. Carvacrol (**12**) and the bromoenone **14** were isolated in 10 and 85% yields, respectively. The latter (**14**) is much more stable than the analogous chloroenone **13**. The ^{1}H NMR spectrum of **14** is very similar to that of **13**. A multiplet (doublet of triplet) signal at δ 4.19 ppm (J = 4.4 and 10.2 Hz) is due to the methine proton at the bromine-bearing carbon (C5) while a broad singlet at δ 5.97 ppm is clearly due to the olefinic proton at C2. The specific rotation of **14** was measured to be +42 (c = 0.29, $CHCl_3$), thereby establishing that a significant amount of racemization was not occurring in the conversion of **11** to **14**.

Another thujone-derived cyclopropylcarbinol also proceeded via the *endo*-cleavage pathway when treated with hydrobromic acid. Hydroxy-enone **15**, obtained from Robinson annulation of thujone (**11**) with ethyl vinyl ketone (EVK), was treated with hydrobromic acid in methylene chloride. Bromo-dienone **16** was isolated in 91% yield (Fig. 3). Compound **16** was previously reduced to (+)-β-cyperone (**17**) by tributyltin hydride in an earlier synthesis of (+)-β-cyperone from thujone (2). Thus, a new sequence to (+)-β-cyperone was completed in four steps using ozonation of thujone, Robinson annulation of thujonol (**11**), acid-promoted ring cleavage of **15**, and radical-mediated reduction of **16**.

The formation of **16** is similar to that of **13** and **14**. The ring cleavage reaction generates an unstable intermediate that then rearranges to the more stable dienone **16** with a fully conjugated dienone system (Fig. 4).

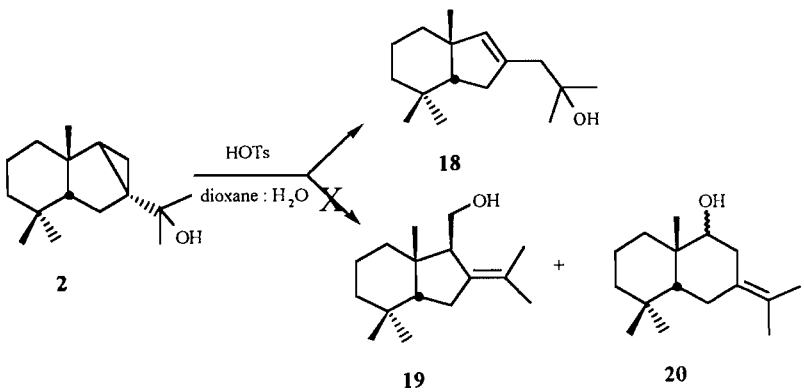
The reason for the *endo*-cleavage selectivity in the thujone-derived intermediates that possess an unsaturated system in ring A, that is, an sp^2-hybridized center at C3, is not well understood. Perhaps the interaction of the double bond *exo* to the bicyclo[3.1.0]hexane and the C1—C5 bond in hydroxy-enone **15** and thujonol (**11**) leads to the weakening of C1—C5 and eventually its facile cleavage under acidic conditions.

The cyclopropylcarbinyl rearrangement

Previous studies have shown that 1-alkyoxymethyl bicy-

clo[3.1.0]hexanes can be cleaved through the *endo*-cleavage pathway by using non-nucleophilic conditions. There are examples in the literature showing the use of other solvolysis conditions (5). The poor nucleophilicity of the attacking groups such as H_2O and HOAc under this set of conditions may allow the ring cleavage reaction to occur in a less synchronized mechanism so that, in the transition state, the C—C bond cleavage to a carbocationic species becomes more predominant than bond formation between the carbon atom and the incoming nucleophile. The *endo*-type cleavage proceeds through a more stable transition state because the tertiary center C5 accommodates the developed partial charge better than the secondary center C6. Therefore, the *endo*-type cleavage prevails.

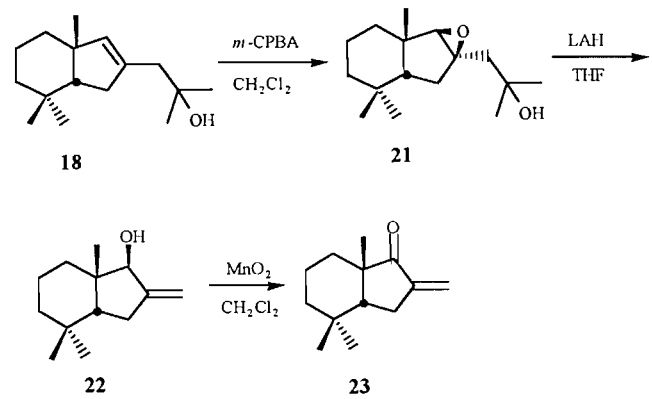
When the thujone-derived cyclopropylcarbinol **2** was treated with a catalytic amount of *p*-toluenesulfonic acid in dioxane:H_2O (1:1), a novel rearrangement product **18** was obtained in 85% yield. The two expected *exo*- and *endo*-cleavage products **19** and **20** were not isolated. The absence of any signals at δ 3.0–4.0 ppm in the NMR spectrum clearly revealed that the product obtained could not be a primary or secondary alcohol. The ^1H NMR spectrum contained a one-proton broad singlet at δ 5.33 ppm corresponding to the olefinic proton, and five methyl singlets at δ 0.87, 1.01, 1.17, 1.21, and 1.22 ppm. From the chemical shifts, it is obvious that none of the methyl groups is adjacent to the double bond.



2 **18** **19** **20**

To confirm the structure of **18**, a series of chemical conversions was carried out. Treatment of **18** with *m*-CPBA in methylene chloride produced a crystalline epoxide **21** in 90% yield. The NMR spectrum showed that the singlet olefinic signal at δ 5.33 ppm is replaced by the proton signal of the epoxide ring at δ 2.85 ppm. The orientation of the epoxide in **21** and, in turn, confirmation of the structure **18** were subsequently established by the X-ray crystal analysis of **21** (Fig. 5). The *cis* A/B ring junction in **21** and the β-orientation for the epoxide ring are clearly revealed. Details of the X-ray analysis will be published elsewhere.

When epoxide **21** was further treated with LAH in THF, an unexpected product, the allylic alcohol **22**, was obtained in



18 **21** **22** **23**

almost quantitative yield. The mass spectrum showed its molecular ion peak at *m/z* 194, corresponding to a loss of an acetone molecule (*m/z* = 58) from **21**. The IR spectrum displayed hydroxyl absorptions at 3100–3650 cm^{-1} while the ^1H NMR spectrum indicated only three methyl singlets at δ 0.82, 1.02, and 1.14 ppm, a one-proton singlet at δ 3.80 ppm corresponding to the allylic tertiary proton α to the hydroxyl group, and two olefinic one-proton singlets at δ 5.06 and 5.21 ppm. The β orientation of the hydroxyl group in **22** is clear from the mechanistic argument shown in Fig. 6.

Allylic alcohol **22** was subjected to allylic oxidation by manganese dioxide (7) in methylene chloride at room temperature to provide enone **23** in 70% yield. The mass spectrum showed the molecular ion peak at *m/z* 192. Its UV spectrum in methanol displayed an intense absorption at 235 nm (log ε = 4.0) and a weaker one at 278 nm (log ε = 2.5). The IR spectrum indicated a conjugated carbonyl absorption at 1710 cm^{-1}. The ^1H NMR spectrum confirmed the disappearance of the allylic tertiary proton signal previously noted in the spectrum of **22**.

To achieve a more conventional hydride-catalyzed opening of the epoxide, the β orientation of the epoxide ring in **21** dictates hydride attack from the very hindered concave α face. Consequently, the fragmentation reaction shown in Fig. 6 becomes the exclusive pathway. The epoxide **21** was treated with "superhydride" (lithium triethylborohydride) in order to see if the reduction rather than the fragmentation would take place. Again, the allylic alcohol **22** was obtained as the only product.

The rearrangement from **2** to **18** is a mechanistically novel process, a stepwise description of which is shown in Fig. 7. Initially the cyclopropylcarbinyl cation (i) is formed by a proton-catalyzed elimination of the hydroxyl group in **2**. The following 1,3-shift of the methylene on the cyclopropane ring would result directly in a spiro-cyclopropylcarbinyl cation (ii). The alternative rearrangement, via the cyclobutyl carbocation indicated, could also afford the cation (ii). This cat-

Fig. 5. Single crystal X-ray structure of epoxide **21** (PLUTO drawing).

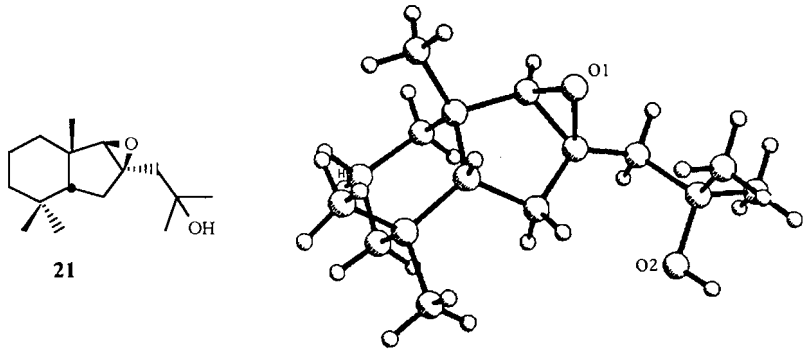


Fig. 6. Mechanism of the fragmentation of epoxide **21**.

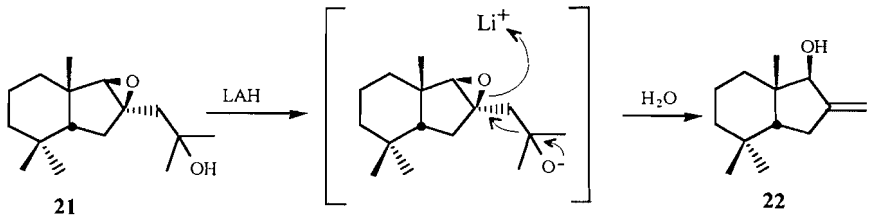
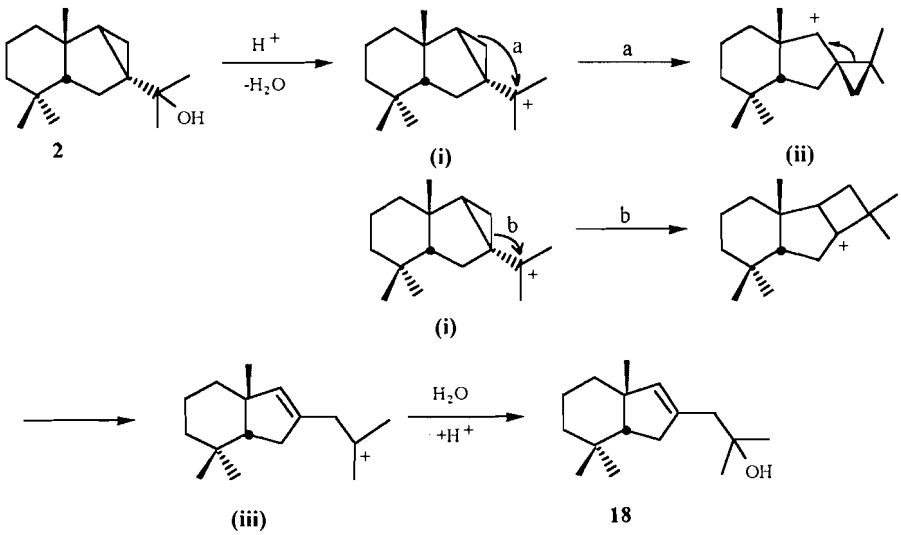


Fig. 7. The mechanism of the cyclopropylcarbinyl rearrangement reaction.



ion (ii) further cleaves regioselectively to form a more stable homoallylic cation (iii) and the latter, upon reaction with water, converts to **18**. The particular transformation between two cyclopropylcarbinyl cations in a manner similar to that between (i) and (ii), normally referred to as the cyclopropylcarbinyl rearrangement, was also termed as the "cyclopropane sliding reaction" by a Japanese group who studied this type of transformation in greater detail with their system (8). Mechanistic proposals involving this interesting reaction are also available in the literature (9) It seems that the thermodynamic stabilities among three carbocations (i), (ii), and (iii) determine the outcome of the solvolysis reaction.

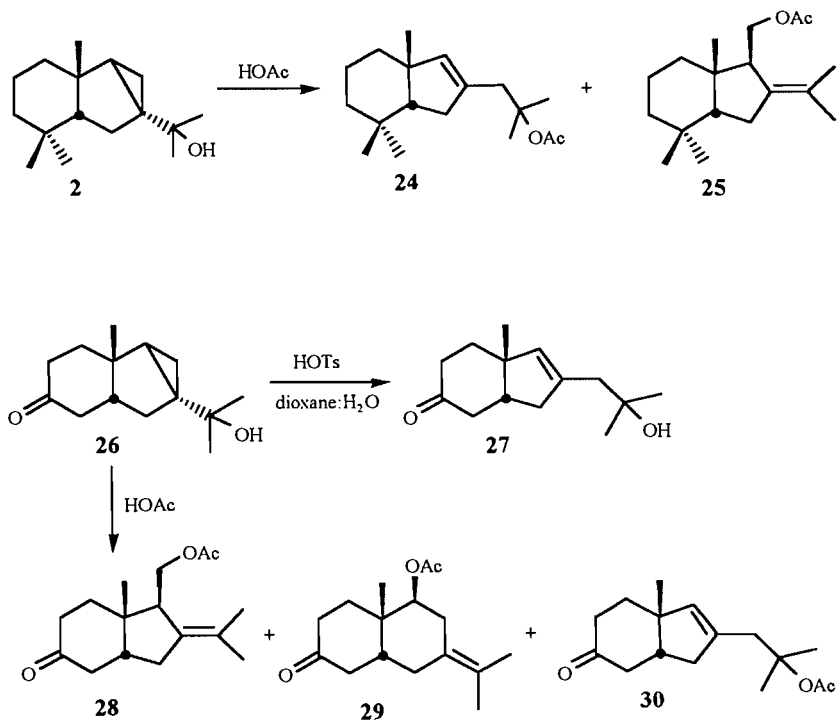
Acetic acid treatment of **2** at 85°C also produced the cyclopropylcarbinol rearrangement product **24** in 60% yield in addition to the *exo*-cleavage product **25** in 6% yield. The competition of *exo* cleavage in this case is likely, because **25** may only slowly convert to the cyclopropylcarbinyl-like cation (i) shown in Fig. 7 once it is formed. The *exo*-cleavage product **19** could not be isolated in the previous reaction. The ^{1}H NMR spectrum of **24** is similar to that of **18**, except that an additional three-proton signal at δ 1.97 ppm due to the acetyl group was noted. For the minor product **25**, a two-proton multiplet (octet) signal at δ 3.92–4.25 ppm, which has a splitting pattern characteristic of the A/B portion of an ABX

system, can be assigned to the methylene attached to the acetate group.

The rearrangement reaction is applicable to other thujone-derived cyclopropylcarbinols but rather specific conditions are required. For example, ketol **26** was converted into product **27** in 87% yield by employing a catalytic amount of *p*-toluenesulfonic acid in a dioxane:water (1:1) mixture. However, rather surprisingly, treatment of **26** with acetic acid gave mainly the *exo*-cleavage product **28** (56%) and the *endo*-cleavage product **29** (14%). Although a very minor peak at δ 5.17 ppm in the ^{1}H NMR spectrum of **28** indicated a possible presence of the rearrangement product **30**, the very minor amount prevented its isolation.

Summary

In summary, acid-promoted ring cleavage reactions of thujone-derived cyclopropylcarbinols proceed through three distinct pathways, including the *exo* cleavage, *endo* cleavage, and the novel cyclopropylcarbinyl rearrangement reaction. Both reaction conditions and substrate structures influence which pathway becomes dominant. The availability of these diverse cleavage patterns allows a more versatile utilization of such thujone-derived cyclopropylcarbinols as chiral synthetic intermediates in subsequent synthetic routes to various natural products and related compounds.



Experimental

Commercially available reagent grade solvents were used for chromatography without further purification. Unless otherwise stated, all reaction products were purified by "flash chromatography" using silica gel (230–400 mesh) supplied by E. Merck Co. with air pressure to obtain a suitable flow (10). Thujone was distilled from Western red cedar leaf oil, which was generously donated by Intrinsic Research and Development Incorporated.

Melting points were measured using a Kofler block melting point apparatus and are uncorrected. Optical rotations were recorded on a Perkin–Elmer 141 automatic polarimeter in chloroform solution using a quartz cell of 10 cm path length with the concentration (in g/100 mL) given in parentheses. The ultraviolet spectra were recorded on Cary 15 or Perkin–Elmer Lambda 4B UV/VIS spectrometers using quartz cells of 1 cm path length. The infrared spectra were recorded on Perkin–Elmer 710, 710B, and 1710 spectrometers in chloroform solution using NaCl cells of 0.1 mm path length or as thin film using NaCl plates. The ^{1}H NMR spectra were obtained from Bruker WH-400 or Varian XL-300 spectrometers with deuteriochloroform as solvent and the chemical shifts are reported in the delta (δ) scale in ppm relative to tetramethylsilane. The low- and high-resolution mass spectra were recorded on AEI-MS-9 and KRATOS-MS-50 spectrometers, respectively, using the electron impact ionization method while the chemical ionization mass spectra were recorded on a Delsi Nermag R10-1 OC spectrometer using ammonia as carrier gas. Elemental analyses were performed by Mr. P. Borda, Microanalytical Laboratory, University of British Columbia.

Chloride 3: the *exo* cleavage

Alcohol **2** (100 mg, 0.420 mmol) in methylene chloride (5.0 mL) was stirred with concentrated hydrochloric acid (5.0 mL) at room temperature for 30 min. Separation and concentration of the methylene layer gave the crude product, which was chromatographed with ethyl acetate:hexanes (1:8, v/v) to afford **3** as a colorless oil (92 mg, 85%).

The physical properties of **3** are as follows: $[\alpha]_D^{25}$ +33.5

(c = 1.00, $CHCl_3$). IR ν_{max} (film): 2910 (C-H stretching) cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ: 0.75–1.85 (22H, m, including 0.84 (3H, s), 1.04 (3H, s), 1.22 (3H, s), 1.63 (3H, s), and 1.70 (3H, s)), 2.04–2.55 (3H, m), 3.40–3.75 (2H, m). MS *m/z*: 256/254 (M^+, 4.8/14.8%), 241 (12.8%), 239 (37.6%), 203 (96.4%), 109 (100%). High-resolution mass measurement: calcd. for $C_{16}H_{27}{}^{37}Cl$: 256.1772; found: 256.1763; calcd. for $C_{16}H_{27}{}^{35}Cl$: 254.1801; found: 254.1801.

Chloroketone 6: the *exo* cleavage

Ketol **5** (78 mg, 0.33 mmol) in methylene chloride (5.0 mL) was stirred with concentrated hydrochloric acid (5.0 mL) at room temperture for 30 min. Water (20 mL) was added to quench the reaction. After methylene chloride extraction (2 × 10 mL), drying over magnesium sulfate, and evaporation of solvent in vacuo, the crude product was chromatographed with ethyl acetate:hexanes mixture (1:8, v/v) to afford the starting ketol **5** (15 mg, 19%) and chloride **6** (51 mg, 74%).

The physical properties of **6** are as follows: $[\alpha]_D^{25}$ +1.4 × 10^2 (c = 0.50, $CHCl_3$). IR ν_{max} (film): 1700, 1641 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ: 1.00 (3H d, J = 7.0 Hz), 1.05 (1H, m), 1.24 (1H, m), 1.44 (3H, s), 1.58–1.80 (7H, including 1.60 (3H, s) and 1.71 (3H, s)), 2.10 (6H, m), 3.45–3.65 (2H, m). MS *m/z*: 256/254 (M^+, 0.6%/2.2%), 239 (0.5%), 218 (34.6%), 203 (18.4%), 133 (85.0%), 41 (100%). High-resolution mass measurement: calcd. for $C_{15}H_{23}O^{35}Cl$: 254.1437; found: 254.1437; calcd. for $C_{15}H_{23}O^{37}Cl$: 256.1408; found: 256.1412.

Carvacrol (12) and chloroenone 13: the *endo* cleavage

Thujonol (**11**) (500 mg, 2.98 mmol) was treated with concentrated hydrochloric acid (25 mL) in methylene chloride (25 mL) at room temperature for 1.5 h. The methylene chloride solution was separated, dried over magnesium sulfate, and concentrated *in vacuo*. Column chromatography with ethyl acetate:hexanes (1:20, v/v) provide chloro-enone **13** (252 mg, 45%) and carvacrol (**12**) (177 mg, 40%).

The physical properties of **12** are as follows: IR (film) ν_{max}: 3400 (O-H stretching) cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ: 1.22 (6H, d, J = 6.6 Hz), 2.21 (3H, s), 2.82 (1H, septet, J = 6.6 Hz), 3.96 (1H, bs), 6.66 (1H, d, J = 1.8 Hz), 6.72 (1H, dd, J = 1.8 and 7.1), 7.04 (1H, d, J = 7.1 Hz). MS *m/z*: 150 (M^+, 35.5%), 135 (100%), 107 (15.6%). High-resolution mass measurement: calcd. for $C_{10}H_{14}O$: 150.1045; found: 150.1051.

The physical properties of **13** are as follows: IR (film) ν_{max} 1675 (C=O stretching), 1630 (C=C stretching) cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ: 1.09 (6H, d, J = 7.2 Hz), 1.30 (3H, d, J = 7.8 Hz), 2.43 (1H, septet, J = 7.2 Hz), 2.54 (1H, m), 2.78 (2H, m), 4.06 (1H, dt, J = 4.4 and 9.8 Hz), 5.95 (1H, bs) ppm. MS *m/z*: 188/186 (M^+, 5.8%/19.1%), 151 (100%), 135 (15.9%).

Carvacrol (12) and bromoenone 14: the *endo* cleavage

Thujonol (**11**) (600 mg, 3.57 mmol) in methylene chloride (25 mL) was stirred with concentrated (48%) hydrobromic acid (25 mL) for 1.5 h at room temperature. The organic layer was separated, dried over magnesium sulfate, and concentrated in vacuo. The crude product was purified by column chromatography using ethyl acetate:hexanes (1:15, v/v) mixture to provide bromoenone **14** (700 mg, 85%) and carvacrol (**12**) (51 mg, 10%).

The physical properties of **14** are as follows: $[\alpha]_D^{25}$ +42 (c = 0.29, $CHCl_3$). UV (MeOH, c = 20 mg/L) λ_{max}: 234 nm (log ε = 3.95). IR (film) ν_{max}: 1670 (C=O stretching), 1630 (C=C stretching) cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ: 1.11 (6H, d, J = 6.8 Hz), 1.34 (3H, d, J = 7.1 Hz), 2.43 (1H, septet, J = 6.8 Hz), 2.55 (1H, m), 4.19 (1H, dt, J = 4.4 and 10.2 Hz), 5.97 (1H, bs). MS *m/z*: 232/230 (M^+, 1.1%/1.3%), 151 (100%), 135 (33.6%), 123 (60.2%). High-resolution mass measurement: calcd. for $C_{10}H_{15}O^{81}Br$ and $C_{15}H_{15}O^{79}Br$: 232.0287 and 230.0130; found: 232.0280 and 230.0116.

Hydroxyenone 15: Robinson annulation

To 1-dimethylaminopentan-2-one iodomethane salt (2.84 g, 9.44 mmol) in ethanol (80 mL) was added the solution of ketol **11** (1.43 g, 8.51 mmol) in ethanol (20 mL). After potassium hydroxide (0.92 g, 80% pure, 13 mmol) was added, the mixture was refluxed under nitrogen for 3 h. Concentration of the reaction mixture in vacuo gave a yellow oil that was chromatographed using ethyl acetate:hexanes mixture (1:1, v/v) to provide compound **15** as a colorless oil (636 mg, 32%).

The physical properties of **15** are as follows: $[\alpha]_D^{25}$ +90.3 (c = 2.03, $CHCl_3$). UV (MeOH, c = 40.6 mg/L) λ_{max}: 248 nm (log ε = 4.04). IR (film) ν_{max}: 3200–3600 (O-H stretching), 1645 (C=O stretching) cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ: 0.76 (1H, t, J = 4.7 Hz), 1.11 (3H, s), 1.20 (6H, s), 1.67 (3H, s) ppm. MS *m/z*: 234 (M^+, 1.2%), 216 (31.5%), 201 (48.0%), 173 (34.7%), 59 (100%). High-resolution mass measurement: calcd. for $C_{15}H_{22}O_2$: 234.1619; found: 234.1613.

Bromodienone 16: the *endo* cleavage

Hydroxy-enone **15** (39 mg, 0.17 mmol) in methylene chloride (5 mL) was stirred with concentrated (48%) hydrobromic acid (5 mL) at room temperature for 3 h. The methylene chloride layer was separated and the aqueous layer was extracted with methylene chloride (5 mL). The combined methylene chloride solution was dried over magnesium sulfate and concentrated in vacuo. Column chromatography of the crude product afforded bromo-dienone **16** (45 mg, 91%).

The physical properties of **16** are as follows: $[\alpha]_D^{25}$ +420 (c = 1.00, $CHCl_3$). UV (MeOH, c = 20 mg/L) λ_{max}: 293 nm (log ε = 4.40). IR (film) ν_{max}: 1660 (C=O stretching), 1620 (C=C stretching) cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ: 1.12 (6H, d, J = 6.0 Hz), 1.17 (3H, s), 1.86 (3H, s), 2.00–2.90 (7H, m), 4.14 (1H, dd, J = 6.0 and 10.0 Hz), 6.31 (1H, s). MS *m/z*: 298/296 (M^+, 80.0%/88.5%), 217 (100%), 175 (56.3%). High-resolution mass measurement: calcd. for $C_{15}H_{21}O^{79}Br$: 296.0775; found: 296.0768.

Alcohol 18: the cyclopropylcarbinyl rearrangement

To the solution of alcohol **2** (80 mg, 0.34 mmol) in a dioxane:water mixture solvent (4.00 mL, 1:1, v/v) was added *p*-toluenesulfonic acid hydrate (20 mg, 0.10 mmol, 0.30 equiv.). The mixture was heated at 85°C for 1 h and cooled to room temperature. Water (10 mL) was added and methylene chloride (2 × 10 mL) was used to extract the aqueous solution. The methylene solution was washed with brine (10 mL), dried over magnesium sulfate, and concentrated in vacuo. Column chromatography of the crude product with ethyl acetate:hexanes mixture (1:8, v/v) gave homoallylic alcohol **18** (70 mg, 87%).

The physical properties of **18** are as follows: $[\alpha]_D^{25}$ +45.2 (c = 1.00, $CHCl_3$). IR ν_{max} (film): 3100–3650 (OH stretching)

cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ: 0.88 (3H, s), 1.02 (3H, s), 1.07–1.70 (18H, m, including 1.18 (3H, s), 1.21 (3H, s) and 1.22 (3H, s)), 2.05–2.45 (4H, m), 5.33 (1H, bs). MS *m/z*: 236 (M^+, 0.1%), 218 (1.6%), 203 (5.0%), 178 (7.1%), 163 (100%), 135 (21.1%). High-resolution mass measurement: calcd. for $C_{16}H_{28}O$: 236.2140; found: 236.2145.

Epoxyalcohol 21: epoxidation

To a solution of alcohol **18** (172 mg, 0.729 mmol) in chloroform (5.0 mL) was added *m*-CPBA (243 mg, 80% pure, 11 mmol, 1.5 equiv.). The mixture was stirred at room temperature for 1 h. After addition of methylene chloride (5.0 mL) and washing with sodium bicarbonate solution (10 mL, 10%), the mixture was dried over magnesium sulfate and concentrated in vacuo. Column chromatography of the crude product with ethyl acetate:hexanes mixture (2:8, v/v) gave epoxide **21** (159 mg, 87%).

The physical properties of **21** are as follows: mp: 82–84°C. $[\alpha]_D^{25}$ +56.7 (*c* = 1.00, $CHCl_3$). IR ν_{max} (film): 3700 (O-H stretching) cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ: 0.70–1.70 (24H, m, including 0.80 (3H, s), 0.98 (3H, s), 1.20 (3H, s), 1.24 (3H, s) and 1.31 (3H, s)), 1.75–2.02 (2H, m), 2.04–2.15 (1H, dd, *J* = 7.2 and 13.6 Hz), 2.85 (1H, s). MS *m/z*: 252 (M^+, 0.2%), 234 (4.1%), 219 (6.9%), 194 (17.9%), 179 (19.8%), 161 (19.3%), 123 (100%), 109 (90.4%). High-resolution mass measurement: calcd. for $C_{16}H_{28}O_2$: 252.2089; found: 252.2088. Anal. calcd. for $C_{16}H_{28}O_2$: C 76.14, H 11.18; found: C 76.14, H 1.05.

Allylic alcohol 22: reductive fragmentation by LAH

Epoxide **21** (30.3 mg, 0.583 mmol) in anhydrous THF (1.0 mL) was added in a dropwise manner to a slurry of LAH (18.4 mg) in THF (1.0 mL) under nitrogen. The mixture was then heated at about 70°C (bath temperature) for 2 h. After cooling to room temperature, ethanol (5.0 mL) was added and stirring continued for 10 min. Subsequently, water (15 mL) was added and the resulting mixture was extracted with ethyl acetate (2 × 10 mL). The ethyl acetate solution was dried over magnesium sulfate and concentrated in vacuo. Column chromatography of the crude product with ethyl acetate:hexanes mixture (1:8, v/v) gave allylic alcohol **22** (20 mg, 87%).

The physical properties of **22** are as follows: $[\alpha]_D^{25}$ +5.4 (*c* = 1.00, $CHCl_3$). IR ν_{max} (film): 3100–3650 (O-H stretching), 3060 (C-H stretching, olefinic), 1650 (C=C stretching) cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ: 0.82 (3H, s), 1.02 (3H, s), 1.05–1.72 (13H, m, including 1.14 (3H, s)), 1.78 (1H, t, *J* = 8.8), 2.20–2.60 (2H, m). MS *m/z*: 194 (M^+, 13.1%), 179 (21.6%), 161 (13.0%), 123 (100%), 109 (85.5%). High-resolution mass measurement: calcd. for $C_{13}H_{22}O$: 194.1670; found: 194.1661.

Enone 23: allylic oxidation by MnO_2

Allylic alcohol **22** (29 mg, 0.15 mmol) in methylene chloride (2.0 mL) was treated with manganese dioxide (65 mg, 0.75 mmol). The slurry was stirred at room temperature for 72 h. After filtering the slurry and washing with methylene chloride (10 mL), the methylene chloride solution was concentrated in vacuo. Column chromatography of the crude product gave enone **23** (8.0 mg, 67% based on recovery) and starting allylic alcohol **22** (17 mg, 59% recovery).

The physical properties of **23** are as follows: $[\alpha]_D^{25}$ +57 (*c* = 0.58, $CHCl_3$). UV (MeOH), *c* = 23 mg/L) λ_{max}: 235 nm (log ε = 4.0), 278 (log ε = 2.5). IR ν_{max} (film): 1710 (C=O stretching), 1635 (C=C stretching) cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ: 0.75–1.70 (16H, m, including 0.85 (3H, s), 1.07 (3H, s), and 1.22 (3H, s)), 2.35–2.65 (2H, m), 5.37 (3H, bs), 6.07 (3H, bs). MS *m/z*: 192 (M^+, 49.9%), 177 (20.3%), 149 (28.9%), 123 (80.7%), 68 (100%). High-resolution mass measurement: calcd. for $C_{13}H_{20}O$: 192.1514; found: 192.1515.

Acetates 24 and 25: the cyclopropylcarbinyl rearrangement

A solution of alcohol **2** (60 mg, 0.26 mmol) in acetic acid (2.5 mL) was heated at 65°C for 2 h. After cooling to room temperature, methylene chloride (10 mL) was added and the mixture was extracted with 10% sodium bicarbonate solution (10 mL). The methylene chloride solution was dried over magnesium sulfate and concentrated in vacuo. Column chromatography of the crude product with ethyl acetate:hexanes mixture (1:25, v/v) yielded acetate **24** (41 mg, 60% based on recovery), acetate **25** (4.0 mg, 6% based on recovery), and the starting alcohol **2** (2.9 mg, 5%).

The physical properties of **24** are as follows: $[\alpha]_D^{25}$ +41.7 (*c* = 1.00, $CHCl_3$). IR ν_{max} (film): 1735 (C=O stretching), 1650 (C=C stretching) cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ: 0.85 (3H, s), 1.00 (3H, s), 1.03–1.60 (16H, including 1.15 (3H, s), 1.38 (3H, s), and 1.45 (3H, s)), 1.97 (3H, s), 2.02–2.35 (2H, m), 2.39–2.62 (2H, AB type, *J* = 7.2 Hz), 5.26 (1H, s). MS *m/z*: 218 (M−HOAc, 37.0%), 203 (100%), 175 (16.7%), 147 (21.5%). High-resolution mass measurement: calcd. for $C_{16}H_{26}$ ($C_{18}H_{30}O_2$ − HOAc): 218.2034; found: 218.2030. Chemical ionization (NH_3 as carrier gas): 279 ($M + H^+$), 219, 203.

The physical properties of **25** are as follows: $[\alpha]_D^{25}$ +63 (*c* = 0.20, $CHCl_3$). IR ν_{max} (film): 1730 (C=O stretching) cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ: 0.75–1.80 (22H, m, including 0.85 (3H, s), 1.03 (3H, s), 1.14 (3H, s), 1.61 (3H, s) and 1.69 (3H, s)), 2.01 (3H, s), 2.10–2.32 (2H, m), 2.39 (1H, t, *J* = 5.6 Hz). MS *m/z*: 278 (M^+, 0.3%), 218 (26.0%), 203 (100%). High-resolution mass measurement: calcd. for $C_{18}H_{30}O_2$: 278.2246; found: 278.2248.

Ketol 27: the cyclopropylcarbinyl rearrangement

To the solution of ketol **26** (82 mg, 0.37 mmol) in a dioxane:water mixture solvent (4.00 mL, 1:1, v/v) was added *p*-toluenesulfonic acid hydrate (22 mg, 0.11 mmol, 0.30 equiv.). The mixture was heated at 85°C for 3.8 h. After cooling to room temperature, the mixture was diluted with water (10 mL) and extracted with methylene chloride (2 × 10.0 mL). The methylene solution was extracted with brine (10 mL), dried over magnesium sulfate, and concentrated in vacuo. Column chromatography of the crude mixture with ethyl acetate:hexanes mixture (2:17, v/v) gave product **27** (72 mg, 87%).

The physical properties of **27** are as follows: $[\alpha]_D^{25}$ + 111 (*c* = 1.00, $CHCl_3$). IR ν_{max} (film): 3050–3650 (O-H stretching), 1700 (C=O stretching), 1650 (C=C stretching) cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ: 1.10–1.90 (13H, m, including 1.20 (3H, s) and 1.23 (6H, two singlets)), 1.95–2.60 (7H, m), 2.75 (1H, dd, *J* = 8.8 and 17 Hz), 5.20 (1H, bs). MS *m/z*: 222 (M^+, 2.8%), 204 (13.6%), 189 (10%), 147 (100%), 133 (34.6%), 106 (47.4%). High-resolution mass measurement: calcd. for $C_{14}H_{22}O_2$: 222.1620; found: 222.1618.

Keto-acetates 28 and 29

A solution of alcohol **26** (65.2 mg, 0.294 mmol) in acetic acid (2.5 mL) was heated at 85°C for 2 h. After cooling to room temperature, methylene chloride (10 mL) was added and the mixture was extracted with 10% sodium bicarbonate solution (10 mL). The methylene chloride solution was dried over magnesium sulfate and concentrated in vacuo. Column chromatography of the crude product with hexanes:ethyl acetate (1:8, v/v) yielded acetate **27** (44 mg, 56%) and acetate **28** (11 mg, 14%).

The physical properties of **28** are as follows: $[\alpha]_D^{25}$ + 63.0 (c = 1.00, $CHCl_3$). IR $\nu_{max.}$ (film): 1735 (C=O stretching of the acetate group), 1705 (C=O stretching) cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ: 1.28 (3H, s), 1.50–1.85 (8H, m, including 1.59 (3H, s) and 1.70 (3H, s)), 1.92 (1H, m), 2.06 (3H, s), 2.10–2.60 (7H, m), 3.95–4.20 (2H, m). MS *m/z*: 264 (M^+, 0.1%), 204 (23.6%), 189 (13.2%), 147 (100%), 134 (85.1%), 119 (44.4%). High-resolution mass measurement: calcd. for $C_{16}H_{24}O_3$: 264.1725; found: 264.1720.

The physical properties of **29** are as follows: $[\alpha]_D^{25}$ = + 30 (c = 0.66, $CHCl_3$). IR $\nu_{max.}$ (film): 1710 (C=O stretching) cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ: 1.17 (3H, s), 1.40–1.80 (8H, m, including 1.65 (3H, s), and 1.72 (3H, s)), 1.90–2.80 (12H, m, including 2.10 (3H, s)), 5.19 (1H, dd, J = 4.2 and 10.2 Hz). MS *m/z*: 204 (M − HOAc, 43.5%), 189 (19.2%), 147 (91.9%), 133 (100%), 119 (54.4%), 105 (51.2%). High-resolution mass measurement calcd. for $C_{14}H_{20}O$ (M − HOAc): 204.1514; found: 204.1508. Chemical ionization (NH_3): 282 ($M + NH_4^+$), 265 ($M + H^+$), 222 ($M - HOAc + NH_4^+$), 205 ($M - HOAc + H^+$).

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