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REGIO AND STEREOSELECTIVE PREPARATION OF SUBSTITUTED CYCLOPENTANONES FROM CYCLOHEXENONES UTILIZING TRIMETHYLSTANNYLLITHIUM AS A KEY REAGENT[1)]

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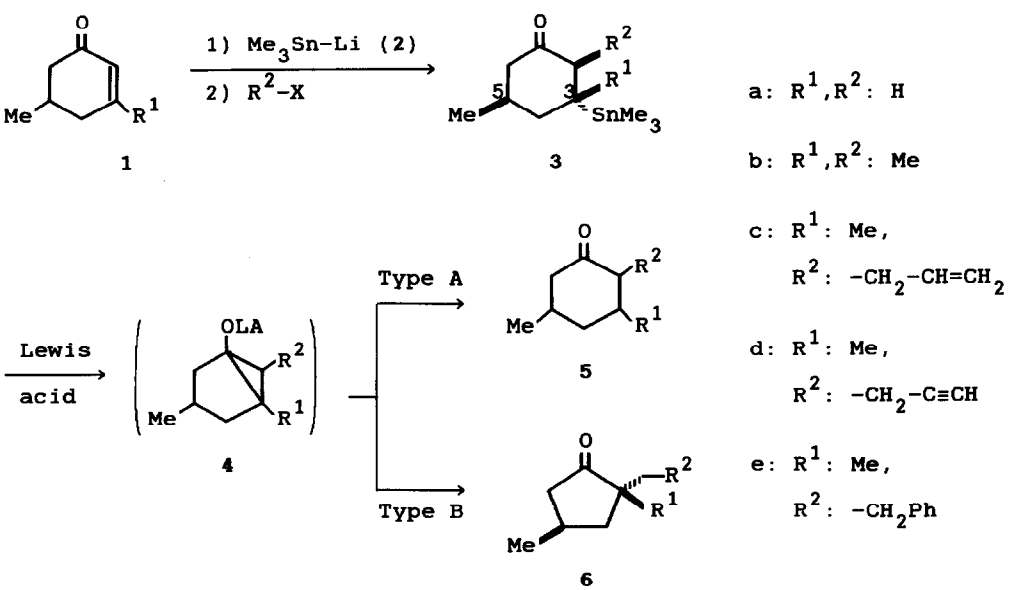
3-Stannylcyclohexanones gave cyclopentanones via carbon-skeleton rearrangement with high regio and stereoselectivity, upon treatment with trimethylsilyl trifluoromethanesulfonate.

In our previous paper,[2)] we described that 3-(trimethylstannyl)-cyclohexanones **3** (R^2 = H or Me, Scheme I) underwent a protonation to produce cyclohexanones **5** and/or cyclopentanones **6**, upon treatment with titanium(IV) chloride. We called the reaction leading to **5** Type A and the reaction leading to **6** Type B.

The results can be summarized as follows. (1) The Type B reaction



Scheme I

occurred exclusively when an alkyl group was present at C3 ($R^1 \neq H$), affording 6 as a single product, while the Type A reaction occurred concurrently with the Type B reaction, affording a mixture of 5 and 6, when no substituent is present at this position ($R^1 = H$). (2) Only single stereoisomers were identified as products, with cyclopentanones 6.

Since the Type B reaction involves a unique carbon-skeleton rearrangement, it is attractive as a potential synthetic method. In order for this reaction to be useful as a synthetic method, two criteria should be fulfilled; chemoselectivity between the Type A and B reactions, and stereoselectivity concerning with the emerging stereogenic centers. The present paper deals with these two problems.

With a view to assure a scope of the Type B reaction, we investigated the effects of C2 substituents (R^2). The stannyl ketones 3a - 3e were obtained by the conjugate addition of 2 to the corresponding cyclohexenones 1, followed by quenching with a) proton, b) methyl iodide, c) allyl bromide, d) propargyl bromide, or e) benzyl bromide, respectively. We found now that, even in cases of compounds carrying an alkyl substituent at C3, the regioselectivity proved to be poor when R^2 contained unsaturated or aromatic group, in contrast to the excellent selectivity when R^2 is hydrogen or methyl. Namely, upon treatment with titanium(IV) chloride, 3c - 3e gave almost equal amounts of cyclohexanones and cyclopentanones, while 3b gave the corresponding cyclopentanone exclusively under the same conditions. In order to improve the selectivity, we investigated the reaction with a variety of Lewis acids. It was found that the selectivity was greatly dependent upon the nature of Lewis acids, and the selective cyclopentanone formation was attained when trimethylsilyl trifluoromethanesulfonate (TMSOTf) was used as a Lewis acid. Remarkably, 3a, which mainly underwent the Type A reaction by titanium(IV) chloride, underwent the Type B reaction exclusively upon treating with TMSOTf.[1] The yields of the formation and the TMSOTf-induced reaction of 3a - 3e are shown in Table 1.

Table 1 Yields of 3 and 6.

Run	Substitution pattern[a]	Product and yield (%)	
		3	6
1	a	98	52
2	b	55	60
3	c	61	64
4	d	95	62
5	e	51	66

a) See Scheme I.

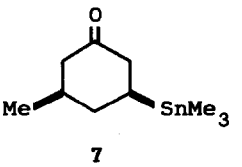
With the chemoselectivity now attained, we next turned our attention to the stereoselectivity. We have proposed that the present reaction proceeds through a cyclopropanol intermediate 4. We have so far assigned the stereochemistry of the

products tentatively based on the findings by Fleming, et al.[3] that the cyclopropane formation via an intramolecular S_N2 reaction proceeds with inversion of the tin-bearing carbon. We now envisioned to assign the stereochemisty of the products in an unambiguous way, and clarify the stereochemical pathway during the carbon-skeleton rearrangement.

It has been known that the addition of stannyl anion to 2-cyclohexenone proceeds exclusively via axial attack, affording products in which the stannyl group occupy the trans position to the substituent at C5.[4] The trapping of the enolate by R^2-X has also been known to take place from the side opposite to the stannyl group. Actually, all the stannyl ketones **3**, obtained from **1b** - **1e**, were revealed to be stereochemically pure by the ^{13}C-NMR, 400 MHz ^{1}H-NMR, and GLC (capillary column) analyses. We assigned the stereostructures for these compounds as indicated in Scheme I, in view of the arguments described above. One exceptional case is that of the reaction from **1a**, which gave, as observed by Kitching et al.,[4] a mixture of **3a** (trans) and **7** (cis) in 3.5 : 1 ratio. We found that the trans/cis ratio is dependent upon the reaction temperature, and the trans formation was favored at the lower temperature as shown in Table 2.

Table 2 Effect of the Conditions upon cis-trans Ratio **3a**/**7**.

Run	Conditions		Product ratio		Combined yield (%)
	Temp(°C)	Time(min)	trans(**3a**)	cis(**7**)	
1	rt	30	3.5	1	81
2	0	15	4.5	1	79
3	0	5	5.8	1	78
4	-78	30	6.6	1	81



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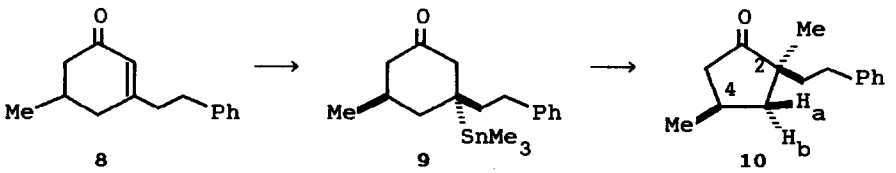
We next tried to elucidate the stereochemical correlation between **3** and **6**. The trans isomer **3a** was isolated in pure state through a preparative gas chromatography of the product from **1a**. When **3a** was treated with TMSOTf, it gave mainly trans isomer **6a**, containing 1/28 amount of cis isomer, as revealed by comparison with a commercial sample (cis : trans = 3 : 1) on GLC (with capillary column) and ^{13}C-NMR analyses.[5] Upon standing at room temperature, the trans-dominant product changed into a cis-dominant mixture, which indicates that the trans isomer **6a** is the less stable kinetic product. Thus, we could almost surely conclude that the trans **3a** afforded trans **6a**. Nevertheless, there remains ambiguity on the stereochemical correlation, because **6a** is an enolizable ketone, and could

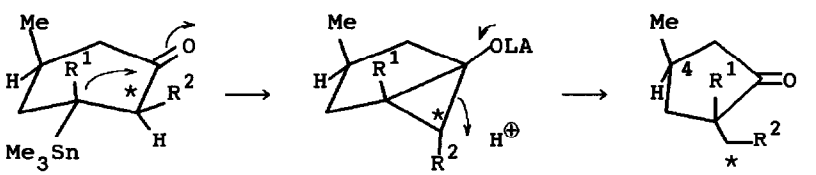
epimerize during the reaction. Therefore, we chose a reaction from 3e to 6e as a more unambiguous system.

Although the achievement of the excellent stereoselectivity observed in this reaction is to be highly evaluated from the synthetic viewpoint, the unavailability of the opposite isomer posed a challenging problem for the assignment of the stereochemistry of 6e. Therefore, we tried to prepare the epimer, and achieved the preparation of 10 through the reaction sequence shown in Scheme II. The fact that no cross formation of these



Scheme II

isomers is observed in the respective reaction (Scheme I and II) is an explicit indication of the excellent stereoselecivity in the present reaction. Since all protons of the two isomers were completely assignable by ^1H - ^1H COSY spectra on 400 MHz ^1H-NMR analyses (see Experimental part), the stereochemical assignment was accomplished by NOESY spectra. Evident interactions were observed for 10 between 2-methyl proton and H_b, and between 4-methyl proton and H_a. The result clearly indicates that the two methyl groups occupy the trans position to each other in 10. The assignment of the stereochemistry certainly confirms our proposal on the reaction scheme that the stannyl ketone 11 undergoes a cyclopropanol formation with inversion of the tin-bearing carbon, followed by bond cleavage to afford cyclopentanone 13 (Scheme III). According to this scheme, the R^2-carrying carbon (asterisked) should occupy trans position to the substituent at C4 in 13, as actually observed.



Scheme III

The accessibility of the substituted cyclopentanones with high selectivities may open up possibilities in organic synthesis. Some of the opportunities are being actively investigated in our laboratory.

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Experimental Section

General Procedure and Instrumentation. GLC experiments were carried out on a 2.5 m × 3 mm stainless steel column packed with silicone SE 30 or Carbowax 20 M on silanized Chromosorb W. Preparative TLC was carried out on DC-Alufolien Kieselgel 60 F_{254}, Art. 5554, using solvents as indicated. Column chromatography was carried out on Kieselgel 60, Art. 7734 (70-230 mesh ASTM) using solvents as indicated. All the spectroscopic data were determined on a pure sample obtained by either distillation, preparative TLC, or column chromatography. ^{1}H-NMR spectra (60 MHz) were recorded on a Hitachi R-24 or JEOL PMX 60 SI spectrometer. ^{1}H-NMR (90 MHz) and ^{13}C-NMR (22.5 MHz) spectra were measured on a Hitachi JNM-PMX 60 S R-90 H spectrometer, and 400 MHz ^{1}H-NMR spectra on a JEOL GSX-400 spectrometer. Unless otherwise stated, the data shown below are those obtained on the 60 MHz machines with CCl_4 solutions. GC-MS spectra were taken on a Shimadzu QP-1000 mass spectrometer, and high resolution mass spectra on a JEOL DX-300 mass spectrometer. IR spectra were recorded on a Shimadzu IR-400 spectrometer.

All of the ^{1}H-NMR signal of the methyl group on tin atom at δ = ~0 ppm accompanied spilitting signals by ^{117}Sn (7.54% abundance, J = 51 Hz) and ^{119}Sn (8.62% abundance, J = 53 Hz).

5-Methyl-3-(2-phenylethyl)-2-cyclohexen-1-one (8). To a Grignard solution, prepared from 2-phenylethyl bromide (1.85 g, 0.01 mol) and Mg (0.365 g, 0.015 mol) in THF (15 ml), was added 3-ethoxy-5-methyl-2-cyclohexen-1-one (1.40 g, 0.01 mol) in 5 ml of benzene-THF (1 : 2), and the mixture was stirred for 3 h at room temperature. The product was poured into ice-water, acidified with 5% HCl, and extracted with ether. Purification on a silica gel column afforded 8 (1.62 g, 76%) in pure state. ^{1}H-NMR, δ 1.00 (d, J = 7 Hz, 3H), 1.70-2.90 (m, 9H), 5.70 (s, 1H), 7.10 (m, 5H). Exact mass, calcd for $C_{15}H_{18}O$ (M): 214.1358, obsvd: 214.1346.

General Procedure for the Preparation of β-Stannyl Ketones 3 and 9. To a THF solution of trimethylstannyllithium (2)[2] (1.5 eq) was added dropwise a THF solution of the corresponding α,β-enone (1 M, 1 eq) at 0 °C under N_2. After stirred for 15 min at 0 °C, the solution was quenched with

water or alkyl halides (1.2 eq). The product was extracted with ether, dried over $MgSO_4$, and the solvent was removed *in vacuo*. Column Chromatography on silica gel (first with hexane and then with $CHCl_3$) gave pure material.

5-Methyl-3-(trimethylstannyl)cyclohexanone (3a and 7). The product was obtained from 5-methyl-2-cyclohexen-1-one (0.232 g, 0.033 mol) in 78% yield (1.68 g) as a cis-trans mixture (see Table 2). The trans isomer was obtained in pure state on a preparative GLC. The spectroscopic data were identical with those reported.[4)]

2,3,5-Trimethyl-3-(trimethylstannyl)cyclohexanone (3b). The product was obtained from 3,5-dimethyl-2-cyclohexen-1-one (0.444 g, 3.58 mmol), followed by quenching with methyl iodide (4.30 mmol) in 55% yield (0.591 g). MS, m/z 304 (M^+), 289, 247, 165 (base peak), 150, 135, 120, 111, 97, 69, 53. ^{1}H-NMR, δ 0.18 (s, 9H), 1.18 (d, J = 7 Hz, 6H), 1.31 (s, 3H), 1.61 ~ 2.95 (m, 6H). ^{13}C-NMR ($CDCl_3$), δ -10.67, 10.34, 21.84, 22.78, 31.13, 31.90, 40.34, 44.37, 51.35, 211.76. Exact mass, calcd for $C_{12}H_{24}OSn$ (M): 304.0849, obsvd: 304.0903.

3,5-Dimethyl-2-(2-propenyl)-3-(trimethylstannyl)cyclohexanone (3c). The product was obtained from 3,5-dimethyl-2-cyclohexen-1-one (0.581 g, 4.69 mmol), followed by quenching with 2-propenyl bromide (2.852 g, 23.6 mmol) in 61% yield (0.943 g). MS, m/z 288 ($M^+ - C_3H_6$), 165 (base peak), 41. ^{1}H-NMR (90 MHz, $CDCl_3$), δ 0.05 (s, 9H), 1.03 (d, J = 5.5 Hz, 3H), 1.19 (s, 3H), 1.55 ~ 2.45 (m, 8H), 4.85 ~ 5.00 (m, 2H), 5.20 ~ 5.90 (m, 1H). ^{13}C-NMR ($CDCl_3$), δ -9.88, 22.54, 23.78, 29.93, 32.60, 33.04, 41.82, 46.21, 58.36, 115.95, 135.41, 211.44.

3,5-Dimethyl-2-(2-propynyl)-3-(trimethylstannyl)cyclohexanone (3d). The product was obtained from 3,5-dimethyl-2-cyclohexen-1-one (0.537 g, 4.33 mmol), followed by quenching with 2-propynyl bromide (2.550 g, 21.4 mmol) in 95% yield (1.342 g). MS, m/z 313 (M^+ - Me), 289 ($M^+ - C_3H_3$), 165 (base peak), 135, 121. ^{1}H-NMR (90 MHz, $CDCl_3$), δ 0.06 (s, 9H), 1.03 (d, J = 5.5 Hz, 3H), 1.17 (s, 3H), 1.55 ~ 2.15 (m, 6H), 2.25 (d, J = 3.0 Hz, 2H), 2,50 (t, J = 3.0 Hz, 1H). ^{13}C-NMR ($CDCl_3$), δ -10.45, 14.52, 21.74, 22.78, 31.44, 32.08, 40.80, 45.00, 56.35, 70.53, 80.62, 208.86.

3,5-Dimethyl-2-benzyl-3-(trimethylstannyl)cyclohexanone (3e). The product was obtained from 3,5-dimethyl-2-cyclohexen-1-one (0.469 g, 3.78 mmol), followed by quenching with benzyl bromide (1.932 g, 11.3 mmol) in 51% yield (0.74g). MS, m/z 365 (M^+ - Me), 289 ($M^+ - PhCH_2$), 165 (base peak), 148, 91($PhCH_2$), 55. ^{1}H-NMR, δ 0.00 (s, 9H), 0.9 ~ 2.2 (m, 12H), 2.6 ~ 3.9 (m, 2H), 7.05 (m, 5H). ^{13}C-NMR ($CDCl_3$), δ -9.78, 22.48, 23.88, 31.78, 32.72, 33.12, 41.99, 46.41, 60.01, 125.99, 128.24, 128.76, 139.10, 211.67.

5-Methyl-3-(2-phenylethyl)-3-(trimethylstannyl)cyclohexanone (9). The

product was obtained from 5-methyl-3-(2-phenylethyl)-2-cyclohexen-1-one (8, 1.050g, 4.92 mmol) in 58% yield (1.070 g). ^{1}H-NMR, δ 0.05 (s, 9H), 1.00 (d, J = 6 Hz, 3H), 1.5 ~ 2.8 (m, 11H).

General Procedure for the Reaction of β-Stannyl Ketones (3) with TMSOTf. To a CH_2Cl_2 solution of β-stannyl ketone 3 (1 M, 1 eq) was added a solution of TMSOTf (0.5 M, 1 eq) in CH_2Cl_2 and the solution was stirred for 15 min at 0 °C under N_2. The reaction was quenched by adding $NaHCO_3$ (sat aq) and the product was extracted with CH_2Cl_2. The crude material obtained by removing the solvent *in vacuo* was chromatographed on silica gel ($CHCl_3$) to give pure material.

2,4-Dimethylcyclopentanone (6a). The product was obtained from 3a (1.21 g, 4.41 mmol) in 51% yield (0.251 g). The trans/cis ratio was 27/1, when trans 3a, obtained by trapping on a preparative GLC, was used as a starting material. The ratio was obtained by comparing with commercial sample on GLC analysis and by referring to the reported spectroscopic data.[5]

2,4-Dimethyl-2-ethylcyclopentanone (6b). The product was obtained from 3b (0.300 g, 0.990 mmol) in 51% yield (0.071 g). MS, m/z 140 (M^+), 112, 96, 70 (base peak), 55. ^{1}H-NMR, δ 0.80 (t, J = 8.0 Hz, 3H), 0.90 (s, 3H), 1.03 (d, J = 5.5 Hz, 3H), 1.10 ~ 2.60 (m, 7H). ^{13}C-NMR ($CDCl_3$), δ 8.42, 20.89, 21.71, 27.38, 29.21, 44.73, 45.89, 50.06, 222.21. Exact mass, calcd for $C_9H_{16}O$ (M): 140.1201, obsvd: 140.1207.

2,4-Dimethyl-2-(3-butenyl)cyclopentanone (6c). The product was obtained from 3c (0.400 g, 1.216 mmol) in 64% yield (0.129 g). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 1.05 (s, 3H, 2-Me), 1.12 (d, J = 6.2 Hz, 3H, 4-Me), 1.29 (dd, J = 13.0 $<H_{3\beta}-H_{3\alpha}>$,[6] 11.0 Hz $<H_{3\beta}-H_4>$, 1H, $H_{3\beta}$), 1.44 (dist.t, J = ~8 Hz, 2H, $H_{1'}$), 1.84 (dd, J = 18.3 $<H_{5\beta}-H_{5\alpha}>$, 11.0 Hz $<H_{5\beta}-H_4>$, 1H, $H_{5\beta}$), 1.94 ~ 2.09 (m, 2H, $H_{2'}$), 2.12 (ddd, J = 13.0 $<H_{3\alpha}-H_{3\beta}>$, 6.9 $<H_{3\alpha}-H_4>$, 2.2 Hz $<H_{3\alpha}-H_{5\alpha}>$, 1H, $H_{3\alpha}$), 2.18 - 2.33 (m, 1H, H_4), 2.49 (ddd, J = 18.3 $<H_{5\alpha}-H_{5\beta}>$, 7.7 $<H_{5\alpha}-H_4>$, 2.2 Hz $<H_{5\alpha}-H_{5\beta}>$, 1H, $H_{5\alpha}$), 4.93 (dq, J = 10.7, 2.2 Hz, 1H, $H_{4'}$), 5.01 (dq, J = 17.2, 2.2 Hz, 1H, $H_{4'}$), 5.77 (ddt, J = 17.2, 10.7, 6.7 Hz, 1H, $H_{3'}$).

2,4-Dimethyl-2-(3-butynyl)cyclopentanone (6d). The product was obtained from 3d (0.394 g, 1.21 mmol) in 62% yield (0.123 g). MS, m/z 164 (M^+), 149, 122, 107, 69. ^{1}H-NMR (400 MHz, $CDCl_3$), δ 1.05 (s, 3H, 2-Me), 1.12 (d, J = 6.2 Hz, 3H, 4-Me), 1.31 (dd, J = 13.4 $<H_{3\beta}-H_{3\alpha}>$, 12.2 Hz $<H_{3\beta}-H_4>$, 1H, $H_{3\beta}$), 1.62 ~ 1.68 (m, 2H, $H_{1'}$), 1.85 (dd, J = 19.2 $<H_{5\beta}-H_{5\alpha}>$, 11.0 $<H_{5\beta}-H_4>$, 1H, $H_{5\beta}$), 1.95 (t, J = 2.6 Hz, 1H, $H_{4'}$), 2.11 ~ 2.21(m, 3H, $H_{3\alpha}$, $H_{2'}$), 2.22 - 2.34 (m, 1H, H_4), 2.50 (ddd, J = 19.2 $<H_{5\alpha}-H_{5\beta}>$, 8.5 $<H_{5\alpha}-H_4>$, 2.2 Hz $<H_{5\alpha}-H_{3\alpha}>$, 1H, $H_{5\alpha}$). ^{13}C-NMR ($CDCl_3$), δ 13.68, 20.71, 21.95, 27.33, 35.34, 45.19, 45.73, 49.36, 68.56, 83.89, 221.17.

(2R*,4R*)-2,4-Dimethyl-2-(2-phenylethyl)cyclopentanone (6e). The

product was obtained from 3e (0.099 g, 0.261 mmol) in 66% yield (0.037 g). MS, m/z 216 (M^+), 201, 112 (base peak), 97, 91. ^{1}H-NMR (400 MHz, $CDCl_3$), δ 1.13 (s, 3H, 2-Me), 1.13 (d, J = 7.5 Hz, 3H, 4-Me), 1.34 (dd, J = 14.0 <$H_{3\beta}$-$H_{3\alpha}$>, 11.8 Hz <$H_{3\beta}$-H_4>, 1H, $H_{3\beta}$), 1.62 ~ 1.68 (m, 2H, $H_{1'}$), 1.87 (dd, J = 18.7 <$H_{5\beta}$-$H_{5\alpha}$>, 11.5 Hz <$H_{5\beta}$-H_4>, 1H, $H_{5\beta}$), 2.19 (ddd, J = 14.0 <$H_{3\alpha}$-$H_{3\beta}$>, 7.7 <$H_{3\alpha}$-H_4>, 2.6 Hz <$H_{3\alpha}$-$H_{5\alpha}$>, 1H, $H_{3\alpha}$), 2.22 ~ 2.35 (m, 1H H_4), 2.47 ~ 2.65 (m, 3H, $H_{2'}$, $H_{5\alpha}$). ^{13}C-NMR ($CDCl_3$), δ 20.82, 22.26, 27.41, 30.55, 38.63, 45.28, 45.86, 49.98, 125.71, 128.09, 128.24, 141.90, 222.24. Exact mass, calcd for $C_{15}H_{20}O$ (M): 216.1514, obsvd: 216.1497.

(2S*,4R*)-2,4-Dimethyl-2-(2-phenylethyl)cyclopentanone (10). The product was obtained from 9 (1.070 g, 2.83 mmol) in 59% yield (0.361 g). MS, m/e 216 (M^+), 200, 112 (base peak), 97, 91, 83. ^{1}H-NMR (400 MHz, $CDCl_3$), δ 1.06 (s, 3H, 2-Me), 1.14 (d, J = 7.3 Hz, 3H, 4-Me), 1.52 (t, J = 12.9 Hz <$H_{3\beta}$-$H_{3\alpha}$, $H_{3\beta}$-H_4>, 1H, $H_{3\beta}$), 1.66 ~ 1.83 (m, 3H, $H_{1'}$, $H_{5\beta}$), 1.92 (ddd, J = 12.9 <$H_{3\alpha}$-$H_{3\beta}$>, 8.2 <$H_{3\alpha}$-H_4>, 2.7 Hz <$H_{3\alpha}$-$H_{5\alpha}$>, 1H, $H_{3\alpha}$), 2.20 ~ 2.33 (m, 1H, H_4), 2.41 and 2.67 (A_2B_2, 2H, $H_{2'}$), 2.50 (ddd, J = 18.8 <$H_{5\alpha}$-$H_{5\beta}$>, 7.7 <$H_{5\alpha}$-$H_{4\beta}$>, 2.7 Hz <$H_{5\alpha}$-$H_{3\alpha}$>, 1H, $H_{5\alpha}$). ^{13}C-NMR ($CDCl_3$), δ 20.47, 22.48, 27.53, 30.90, 39.50, 44.36, 46.71, 50.22, 125.63, 128.15, 142.05, 222.33. Exact mass, calcd for $C_{15}H_{20}O$ (M): 216.1514, obsvd: 216.1498.

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6) The subscripts α and β designate the positions of the protons behind and in front of the plane, respectively, placing the molecule as shown in the respective figures.