A Novel Methylation of Allylic Alcohols Using *cis*-Dichlorobis(triphenylphosphine)platinum(II)–Tin(II) Chloride Dihydrate Complex Catalyst

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The reaction of allylic alcohols in benzene–methanol (3 : 2) solvent in the presence of *cis*-dichlorobis(triphenylphosphine)platinum(II)–tin(II) chloride dihydrate complex catalyst afforded allylic methyl ethers. The structure of the obtained compounds was identified by direct comparison with authentic sample. Cholest-4-en-3α-ol, with a quasi-axial hydroxy group, gave a quantitative yield of 3α-methoxycholest-4-ene. On the other hand, cholest-4-en-3β-ol, with a quasi-equatorial hydroxy group, yielded 3β-methoxycholest-4-ene preferentially, but it also yielded 3α-methoxy compound as a by-product, lowering the selectivity of the reaction.

Allylic alcohol-type compounds exist frequently as important natural products, and their pyrophosphate are biosynthetically key intermediates.[1)]

Although transition metal-catalyzed isomerization of allylic type compounds is known,[2)] methylation of allylic alcohols using a metal complex has not yet been reported.

In our previous paper,[3)] we reported that several steroidal allylic alcohols give allyl ethers when they are made to react with dichlorobis(triphenylphosphine)platinum(II)–tin(II) chloride dihydrate complex catalyst[4)] (Pt–Sn catalyst) in methanol–benzene.

In this paper, we revised the structure of allylic methyl ethers using high resolution ^{1}H NMR and direct comparison with an authentic sample. In addition, we investigated the reactivity of several allylic alcohols.

Results and Discussion

Cholest-4-en-3α-ol (**1**)[5)] was made to react with methanol using Pt–Sn catalyst in benzene or THF at room temperature for 1 h. This reaction gave, almost quantitatively, 3α-methoxycholest-4-ene (**3**) (Scheme 1). On the other hand, the reaction of cholest-4-en-3β-ol (**2**)[5)] under similar conditions for 4 h gave 3β-methoxycholest-4-ene (**4**) in about 75% yield, and compound **3** in about 25% yield.

In addition to **4** and **3**, cholesta-3,5-diene (**5**)[6)] was isolated in a poor yield of about 10% after a prolonged reaction (12 h) in both cases.

The reaction of cholest-5-en-7α-ol (**6**)[7)] under similar conditions gave 7α-methoxycholest-5-ene (**8**), 7β-methoxycholest-5-ene (**9**), and cholesta-4,6-diene (**10**)[6)] in 60, 20, and 20% yield, respectively, after 4 h (Scheme 2). The reaction of cholest-5-en-7β-ol (**7**)[7)] under similar conditions also gave compound **9**, compound **8**, and **10** in about 60, 20, and 20% yield, respectively, after 4 h.[8)] These results are summarized in Table 1.

Compound **4** has a band at 1085 cm^{-1} (OCH_3), 1665 cm^{-1} (C=C) in its IR spectrum. In the ^{1}H NMR spectrum of **4**, the signal of a vinyl proton at 5.37 ppm (br. s, w/2=4.8 Hz) and the signal of a methine proton at 3.69 ppm (w/2=22 Hz). On the basis of these spectral data, it is assumed that the stereochemistry of the methoxy group in the molecule has a β-configuration.

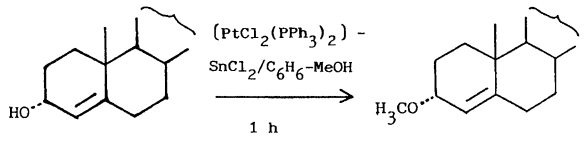
The structure of **4** was confirmed by direct comparison with an authentic sample, 3β-methoxycholest-4-ene,[7,9a,9b,9c)] which was prepared in our laboratory.

To examine the reactivity of **4**, the hydrogenation of **4** with ruthenium black catalyst[10)] was done at room temperature in *t*-butyl alcohol for 1 h to obtain 3β-meth-

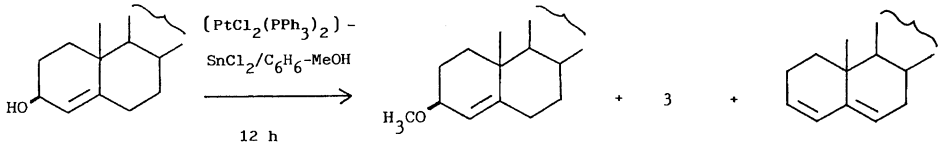
Table 1. Composition of the Products by Platinum Complex Catalyst

Substrates	Reaction time/h	Composition of the products (%)					
		3	**4**	**5**	**8**	**9**	**10**
1	1	100					
1[a)]	3	100					
2	4	25	75				
2	12	22	68	10			
6	4				60	20	20
7	4				20	60	20

a) Catalyst ratio of $PtCl_2(PPh_3)_2 : SnCl_2 \cdot 2H_2O = 0.1 : 1$.

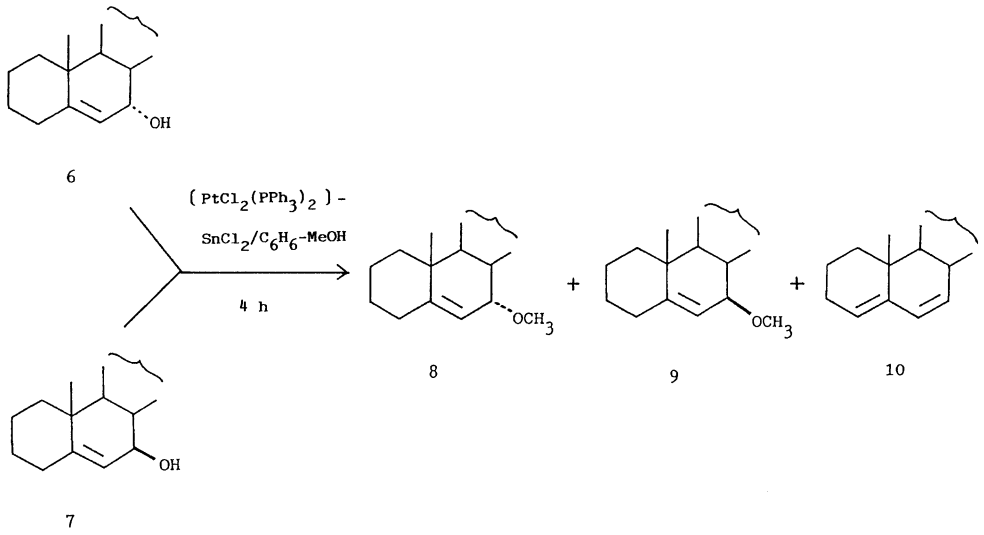


1 3



2 4 5

Scheme 1.



6 8 9 10 7

Scheme 2.

oxycholest-5α-cholestane (**11**) in 93% yield (Scheme 3). In the ^{1}H NMR spectrum of **11**, the signal of a vinyl proton in the compound **4** disappeared. On the basis of the ^{1}H NMR spectrum, it is assumed that **11** is a saturated methoxy compound.

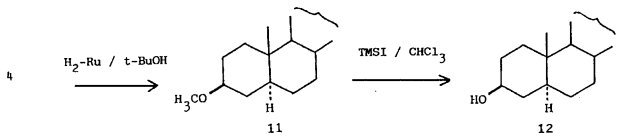
Treatment of **11** with trimethylsilyl iodide (TMSI)[11] in chloroform at room temperature for 18 h gave **12** in 82% yield. The structure of **12** was confirmed by direct comparison with an authentic sample, 5α-cholestan-3β-ol.[12]

Compound **3** has a band at 1085 cm^{-1} (OCH_3), 1665 cm^{-1} (C=C) in its IR spectrum. In the ^{1}H NMR spectrum of **3**, the signal of vinyl proton appeared at 5.39 ppm (1H, d, J=3 Hz) and the signal of methine proton at 3.43 ppm(s). Accordingly, it is assumed that the stereochemistry of the methoxy group on **3** has an α-configuration. By comparison with optical rotation data of **3** and **4**, it is suggested that **3** is a epimer of **4**.

The structure of **3** has been established by direct comparison with the authentic sample, 3α-methoxycholest-4-ene,[9a] which was synthesized in our laboratory.

Compound **9** has a band at 1098 cm^{-1} (OCH_3), 1670 cm^{-1} (C=C) in its IR spectrum. In the ^{1}H NMR spectrum of **9**, the signal of vinyl proton was observed at 5.35 ppm (br. s, w/2=4.2 Hz). In addition, the signal of a methine proton was observed at 3.35 ppm (d, J=10 Hz). On the basis of these spectral data, it is assumed that the stereochemistry of the methoxy group in **9** has a β-configuration.

To confirm the structure of **9**, the hydrogenation of **9** with ruthenium black catalyst in t-butyl alcohol



11 12

Scheme 3.

was carried out for 1 h to produce **13** in 93% yield (Scheme 4). In the ^{1}H NMR spectrum of **13**, the signal of vinyl proton at 5.35 ppm in **9** disappeared. On the basis of the ^{1}H NMR spectrum, it was assumed that **13** was a saturated methoxy compound.

Treatment of **13** with TMSI in chloroform at room temperature for 18 h gave **14** in 80% yield. The structure of **14** was also confirmed by direct comparison with the authentic sample, 5α-cholestan-7β-ol.[13]

Therefore, it was found that **9** has the structure of 7β-methoxycholest-5-ene.

Compound **8** has a band at 1085 cm^{-1} (OCH_3), 1665 cm^{-1} (C=C) in its IR spectrum. In the ^{1}H NMR spectrum of **8**, the signal of a vinyl proton was observed at 5.64 ppm (1H, d, J=3 Hz) and the signal of a methine proton at 3.26 ppm(s), respectively. Accordingly, it is assumed that the stereochemistry of the methoxy group on **8** has an α-configuration. By comparison with optical rotation data of **8** and **9**, it is assumed that **8** is a epimer of **9**. On the basis of these spectral data, it was decided that **8** has the structure of 7α-methoxycholest-5-ene.

Based on these experimental results, it has been presumed that methylation of allylic alcohol with Pt–Sn catalyst in benzene–methanol (3 : 2) proceeded through the formation of a π-allyl complex via cation followed by the attack of methoxide anion.

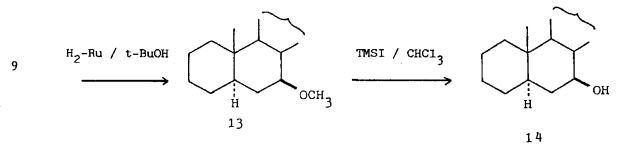
Compound **1** coordinates to the Pt–Sn catalyst from the β-side to form the π-allyl metal complex intermediate via cation. Then, the attack of methoxide anion from the α-side gave selectively compound **3**.

On the other hand, in the case of **2**, the Pt–Sn catalyst coordinated to **2** from the α-side and then a π-allyl metal complex intermediate via cation was formed. Subsequently, the attack of methoxide anion from the β-side in the molecule afford preferentially **4**, but **3** was obtained as by-product owing to steric hindrance of C_{10}-methyl group.

To examine the scope and limitations of allylic alcohols, we attempted to make geraniol (**15**), linalool (**16**), and carveol (**17**) by reaction with Pt–Sn catalyst under similar conditions, but these attempts were unsuccessful (Fig. 1). However, only methoxylation of isophorol(3,5,5-trimethyl-2-cyclohexen-1-ol) (**18**) with Pt–Sn catalyst under the similar conditions afforded 1-methoxy-3,5,5-trimethyl-2-cyclohexene (**19**) in 91% yield.

At the present stage, we found that α,β-unsaturated cyclic alcohols with an alkyl substituent at β-position are selectively reactive under these conditions.

We assumed that substitution of a hydroxy group of



Scheme 4.

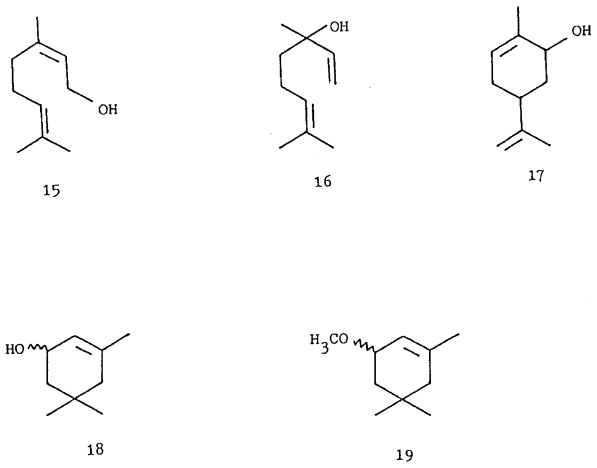


Fig. 1.

the allylic alcohol by a methoxy group proceeds via a π-allyl complex similarly to allylic substitution by palladium complex catalyst.[14]

Experimental

All melting points are uncorrected. IR spectra were obtained in KBr on a Hitachi 270-50 IR instrument. ^{1}H NMR spectra were measured at 100 and 270 MHz, with deuteriochloroform as the solvent. Chemical shifts are given in ppm, with tetramethylsilane (TMS) as an internal standard (JNM-FX100 and GX270 instruments). Mass spectra were recorded on a Hitachi M-80B system at 70 eV. Optical rotation were measured on a Horiba SEPA-200 polarimeter. Thin layer chromatography was recorded on an Iatroscan TH-10 instrument.

Materials, Authentic Specimens, and Complex Catalyst. *cis*-Dichlorobis(triphenylphosphine)platinum-(II) was prepared by Bailar's method.[4a,4b] Tin(II) chloride dihydrate ($SnCl_2 \cdot 2H_2O$) was from a commercial source (Wako Pure Chemical Industries Ltd.)

Reduction of cholest-4-en-3-one with $LiAlH_4$ in dry ether gave cholest-4-en-3α-ol (**1**)[5] (mp 82—83 °C) and cholest-4-en-3β-ol (**2**)[5] (mp 129—130 °C).

Hydrogenation of cholesta- 3, 5- dien- 7- one[13a] with rhodium complex catalyst in benzene–ethanol (1 : 1) afforded cholest- 5- en- 7- one[13a] and then reduction of the hydrogenation product with $NaBH_4$ in methanol yielded cholest-5-en-7α-ol (**6**),[7] (mp 62—63 °C) and cholest-5-en-7β-ol (**7**),[7] (mp 87—88 °C). Reduction of isophorone with $LiAlH_4$ in dry ether gave isophorol(3,5,5-trimethyl-2-cyclohexen-1-ol) (**18**).

Reaction of 2 with Pt–Sn Catalyst. To a solution of *cis*-[$PtCl_2(PPh_3)_2$] (1.02 g, 1.3 mmol) and $SnCl_2 \cdot 2H_2O$ (2.9 g, 13 mmol) in benzene–methanol (3 : 2) (25 ml), cholest-4-en-3β-ol (**2**), (0.5 g, 1.3 mmol) was added and stirred for 4 h at room temperature. After reaction ceased, the solvent was evaporated under reduced pressure and then the residue was added to water. The mixture was extracted with benzene, and the benzene layer was washed with water. The organic layer was dried over anhydrous Na_2SO_4, and evaporation of benzene gave a residue. A portion of the residue was chromatographed on aluminum oxide. Elution with hexane afforded 3α-methoxycholest-4-ene (**3**)[9a] as a glassy solid, [α]$_D$

+71.1° (c=4.10, EtOH); IR (KBr) 1665 (C=C), 1085 cm^{-1} (OCH_3); MS m/z 400 (M^+; $C_{28}H_{48}O$); ^1H NMR ($CDCl_3$) δ=5.39 (1H, d, J=3 Hz, CH=C), 3.43 (1H, s, CH–OCH_3), 3.28 (3H, s, OCH_3). Elution with hexane–benzene (10:1) gave 3β-methoxycholest-4-ene (**4**), which was recrystallized from ether–methanol, mp 70—70.5 °C; $[\alpha]_D$ +38.5° (c=0.87, EtOH), (lit, 68—70 °C,[9c] 72—73 °C,[7] $[\alpha]_D$ +39°); IR (KBr) 1665 (C=C), 1085 cm^{-1} (OCH_3); MS m/z 400 (M^+; $C_{28}H_{48}O$); ^1H NMR ($CDCl_3$) δ=5.37 (1H, br. s, w/2=4.8 Hz, CH=C), 3.69 (1H, br. s, w/2=22 Hz, CH–OCH_3), 3.35 (3H, s, OCH_3), while the other portions were analyzed by TLC.

Cholesta-3,5-diene (**5**) (mp 77—78 °C, $[\alpha]_D$ −118° (c=0.56, EtOH), (lit, 75.9—80 °C),[6] $[\alpha]_D$ −103.24°) was isolated after prolonged reaction (12 h) for **2**.

Reaction of 6 with Pt–Sn Catalyst. Cholest-5-en-7α-ol (**6**) was stirred with Pt–Sn catalyst in benzene–methanol (3:2) for 4 h at room temperature. Reaction products were chromatographed on aluminium oxide, using hexane as the eluent, to give cholesta-4,6-diene (**10**) (mp 86—87 °C, $[\alpha]_D$ +47.5° (c=0.64, EtOH), (lit, 84—85 °C,[6] $[\alpha]_D$ +45.77°). Elution with hexane–benzene (10:1) afforded 7α-methoxycholest-5-ene (**8**) which was recrystallized from ether–methanol, mp 77—78 °C; $[\alpha]_D$ −103.1° (c=0.52, EtOH); IR (KBr) 1665 (C=C), 1085 cm^{-1} (OCH_3); MS: m/z 400 (M^+; $C_{28}H_{48}O$); ^1H NMR ($CDCl_3$) δ=5.64 (1H, d, J=3 Hz, CH=C), 3.35 (3H, s, OCH_3), 3.26 (1H, s, CH–OCH_3). Elution with hexane–benzene (10:1.5) gave 7β-methoxycholest-5-ene (**9**) which was recrystallized from ether–methanol, mp 90—90.5 °C; $[\alpha]_D$ +22.8° (c=0.50, EtOH); IR (KBr) 1670 (C=C), 1098 cm^{-1} (OCH_3); MS m/z 400 (M^+; $C_{28}H_{48}O$), ^1H NMR ($CDCl_3$) δ=5.35 (1H, br. s, w/2=4.2 Hz, CH=C), 3.35 (1H, d, J=10 Hz, CH–OCH_3), 3.26 (3H, s, OCH_3).

Reaction of 18 with Pt–Sn Catalyst. Isophorol (**18**) was made to react for 1 h under similar conditions. The reaction product was chromatographed on aluminium oxide, using hexane as the eluent to give **19** as an oily substance, IR (KBr) 1675 (C=C), 1095 cm^{-1} (OCH_3); ^1H NMR ($CDCl_3$) δ=5.84 (1H, s, CH=C), 3.80 (1H, br. s, w/2=20 Hz, CH–OCH_3), 3.36 (3H, s, OCH_3), 1.69, 0.99, 0.88 (3H×3, s, CH_3); MS m/z 154 (M^+; $C_{10}H_{18}O$).

Hydrogenation of 4. A mixture of **4** (30 mg), ruthenium catalyst (30 mg), and t-butyl alcohol (20 ml) was stirred under hydrogen at ordinary pressure. After the uptake of hydrogen ceased, the catalyst was filtered off and the filtrate was evaporated to dryness under reduced pressure. The recrystallization of the product from methanol afforded 3β-methoxy-5α-cholestane (**11**), yield 28 mg (93%); mp 79—80 °C; $[\alpha]_D$ +24.8° (c=0.46, EtOH) (lit, 82—83 °C),[9b] $[\alpha]_D$ +21.5°); IR (KBr) 1105 cm^{-1} (OCH_3); MS m/z 402 (M^+; $C_{28}H_{50}O$); ^1H NMR ($CDCl_3$) δ=3.67 (1H, br. s, w/2=20 Hz, CH–OCH_3), 3.28 (3H, s, OCH_3), 1.00 (3H, s, 19-CH_3), 0.68 (3H, s, 18-CH_3).

Hydrogenation of 9. A mixture of **9** (30 mg), ruthenium catalyst (30 mg), and t-butyl alcohol (20 ml), was stirred under similar conditions. Recrystallization of the product from ethanol gave 7β-methoxy-5α-cholestane (**13**), yield 28 mg (98%); mp 77—78 °C; $[\alpha]_D$ +60.2° (c=0.43, EtOH); IR (KBr) 1103 cm^{-1} (OCH_3); MS m/z 402 (M^+; $C_{28}H_{50}O$); ^1H NMR ($CDCl_3$) δ=3.70 (1H, br. s, w/2=15 Hz, CH–OCH_3), 3.19 (3H, s, OCH_3).

Reaction of 11 with Trimethylsilyl Iodide (TMSI). To a solution of **11** (10 mg) in chloroform (6 ml), TMSI solution (1 ml) was added and stirred for 18 h at room temperature. After reaction ceased, methanol (3 ml) was added to the mixture, the solvent was evaporated to dryness under reduced pressure, and the residue was added to sodium sulfite solution. The mixture was extracted with ether, and the ethereal solution was washed with 10%-aqueous $NaHCO_3$ solution and water. The extract was dried over anhydrous Na_2SO_4, and evaporation of ether gave a residue. Recrystallization from petroleum ether afforded 5α-cholestan-3β-ol (**12**) yield 7.9 mg (82%); mp 139 °C; $[\alpha]_D$ +20° (c=0.95, EtOH) (lit, mp 142 °C),[12] $[\alpha]_D$ +24°); IR (KBr) 3300 cm^{-1} (OH); MS m/z 388 (M^+; $C_{27}H_{48}O$); ^1H NMR ($CDCl_3$) δ=3.50 (1H, br. s, w/2=21 Hz, CH–OH), 1.02 (3H, s, 19-CH_3), 0.64 (3H, s, 18-CH_3).

Reaction of 13 with TMSI Solution. A mixture of **13** (10 mg), TMSI solution (1 ml), and chloroform (6 ml) was stirred under similar conditions. The recrystallization from petroleum ether yielded 7.7 mg (80%) of 5α-cholestan-7β-ol (**14**), mp 112—113 °C; $[\alpha]_D$ +50° (c=1.1, EtOH) (lit, 112—113 °C),[13] $[\alpha]_D$ +52°).

Methylation of Cholest-4-en-3β-ol (General Procedure). Potassium of (50 mg) and cholest-4-en-3β-ol (90 mg) was shaken in dry benzene under nitrogen at 60 °C for 2 h, thereafter methyl iodide (1.3 ml) was added and the mixture was refluxed for 3 h. The product, isolated in the usual way, was chromatographed on aluminium oxide. Elution with pentane gave 3β-methoxycholest-4-ene (**4**) which was recrystallized from ether–methanol, mp 71—72 °C; $[\alpha]_D$ +38° (c=0.85, EtOH) (lit, mp 72—73 °C,[7] $[\alpha]_D$ +39°).

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8) Here we wish to correct that the yield of **8** changes into 60% and the yield of **9** alters to 20% in methylation of **6** and, in addition, the yield of **8** convert to 20% and the yield of **9** changes into 60% in methylation of **7**, in previous paper.[3]

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