Pergamon

Tetrahedron Vol. 50, No. 2, pp. 475-486, 1994

0040-4020/94 $6.00+0.00

0040-4020(93)E0110-2

A Novel Method for Stereospecific Generation of Natural C-17 Stereochemistry and Either C-20 Epimer in Steroid Side Chains by Palladium-Catalyzed Hydrogenolysis of C-17 and C-20 Allylic Carbonates.

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Abstract: The allylic alcohol, obtained by the reaction of C-17-keto steroid with isopropenyllithium, was converted to carbonate. Its hydrogenolysis with triethylammonium formate affords C-17β-isopropenyl group. Steroid side chain units were introduced by the reaction of C-20 keto steroid with (E) and (Z) alkenyl lithiums.The natural epimer at C-20 in steroid side-chains was generated stereospecifically by the palladium-catalyzed hydrogenolysis with triethylammonium formate of C-20 (Z) allylic carbonates, and the unnatural configuration was generated by the C-20 (E) allylic carbonate.

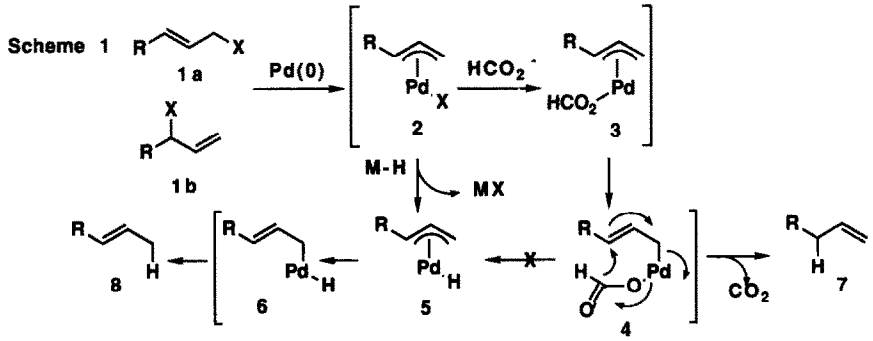
INTRODUCTION

One important problem in the total or partial synthesis of steroids is creation of the correct natural configurations at C-17 and C-20 in a side chain. Particularly important is the construction of C-20 stereochemistry. A number of methods for stereocontrolled construction of C-20 stereochemistry have been reported. The ene reactions of acrylate[1] and propiolate [2,3] with 17(E)-ethylidene derivatives offer good synthetic methods. Wittig rearrangement,[4,5] 3,3-Claisen rearrangement,[6] Carroll rearrangement,[7] and oxy Cope rearrangement [8] of 16-hydroxy-17(E)-ethylidene derivatives are another methods. Stoichiometric and catalytic reactions of π–allylpalladium complexes with soft carbon nucleophiles,[9,10] and hard carbon nucleophiles[11] were carried out. Similar reactions via organo copper reagents are known.[12,13] The alkylation of 21-oic acid esters using the ester group as a precursor of methyl group is stereospecific.[14] Hydroboration of C-20(22) methylene steroids with a hindered borane generates correct stereochemistry.[15] In addition to creation of the natural configuration, preparation of the corresponding unnatural epimer is attracting attention, because steroids which have the unnatural configuration at C-20 possess interesting biological activity different from that of the natural epimers,[16] and methods for the stereoselective preparation of the unnatural epimer are desirable. In particular, efficient preparation of both epimers from a common intermediate is especially desirable. Some of the reactions referred to above offer synthetic routes to the unnatural isomers by the use of stereoisomeric starting materials. However, synthesis of the stereoisomers required for preparing both epimers is not always easy. In this paper we wish to report a simple new method for creating either the natural or unnatural configuration at C-20 at will. Also introduction of β-type C-17 isopropenyl group is presented. The method is based on the palladium-catalyzed hydrogenolysis of C-20 (E) and (Z) allylic carbonates with formic acid.

Preliminary accounts of the work have been published,[17,18] and the details of the studies are presented in this paper.

PALLADIUM-CATALYZED REGIOSELECTIVE HYDROGENOLYSIS OF ALLYLIC COMPOUNDS

The palladium catalyzed reaction of allylic esters with formic acid to give olefins was reported briefly.[19] We found that the palladium-catalyzed hydrogenolysis of terminal allylic compounds **1a,b** with ammonium formate affords terminal olefins **7** with high regioselectivity.[20] Furthermore, reaction proceeds smoothly with higher regioselectivity by the reaction of allylic carbonates with triethylammonium formate.[21,22] Triethylammonium formate is useful for palladium-catalyzed hydrogenolsysis of other substrates.[23-26] The most important feature of this reaction is that the hydride generated from the palladium formate **3** attacks regioselectively the more substituted side of the allylic system by the cyclic mechanism shown by **4** to give terminal olefins **7**. (Scheme 1) We assume that the decarboxylation and hydride transfer should be the concerted process, and formation of the palladium hydride **5** from **4** does not take place. Hydrogenolysis of allylic compounds with other hydrides sources, such as $LiAlH_4$,[27] borohydrides,[28-31] hydrosilanes (polymethylhydrosilane),[32] tin hydride,[33] butylzinc chloride,[34] SmI_2,[35] electrolysis,[36] is possible. But these hydrides form the palladium hydride **5** by transmetallation, and attack the less hindered terminal allylic carbon by reductive coupling of **6** to generate 2-olefins **8** as main products. In this sense, formate is special, and formate method is more useful.

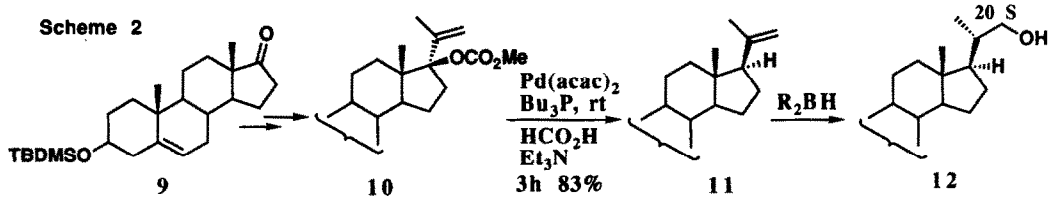


In addition to regioselectivity, we have observed high stereospecificity in the hydrogenolysis of cyclic allylic systems, and have successfully applied the method to the stereospecific generation of *cis* and *trans* ring junctions.[37]

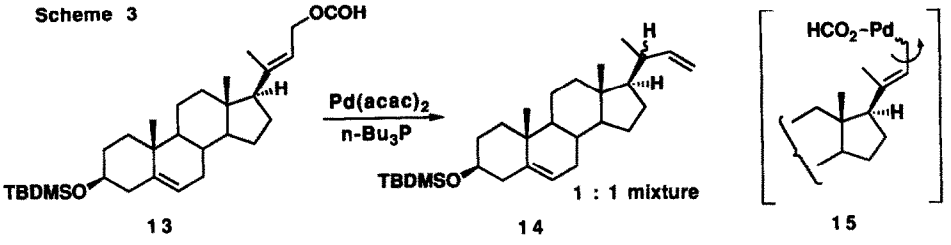
RESULTS

Control of C-17 stereochemistry. We have reported that isopropenyl group, which is present abundantly in terpenoids, can be introduced to ketones by isopropenylation, carbonate formation and hydrogenolysis.[17] Based on this method, we introduced the C-17 isopropenyl group by the reaction of isopropenyllithium with the C-17 keto steroids **9** from the α-side.(Scheme 2) The resulting β-oriented allylic alcohol was converted to

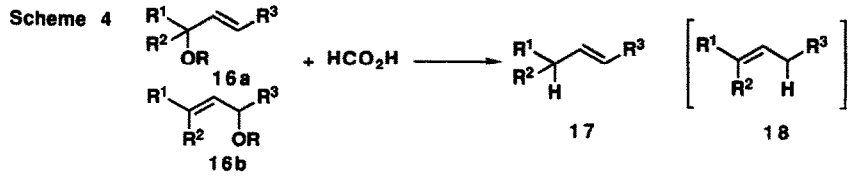
carbonate **10** and the palladium-catalyzed hydrogenolysis of the carbonate with triethylammonium formate at room temperature afforded C-17 isopropenyl steroid **11**. Comparison with an authentic sample showed that **11** has the correct β stereochemistry. It is known that hydroboration of the C-17 isopropenyl group **11** gives the alcohol **12** which has the correct stereochemistry of C-20.[15] By this way, the method of generating the correct stereochemistries at C-17 and C-20 from the C-17 keto steroid **9** was established.[17]



Then we wanted to create the sterochemistry of C-20 by the palladium method. One obvious route is the hydrogenolysis of the C-23 allylic formate **13**. The palladium-catalyzed reaction of the formate **13** afforded the terminal olefin **14** regioselectively. (Scheme 3) But the reaction was not stereoselective. Its ^{1}NMR spectrum shows that the product **14** is a 1:1 mixture of the stereoisomers at C-20. This result is understandable, because the intermediate π-allylpalladium complex **15** can rotate freely and the hydride transfer takes place from both α and β sides to give the both isomers. Thus this attempt was unsuccessful.



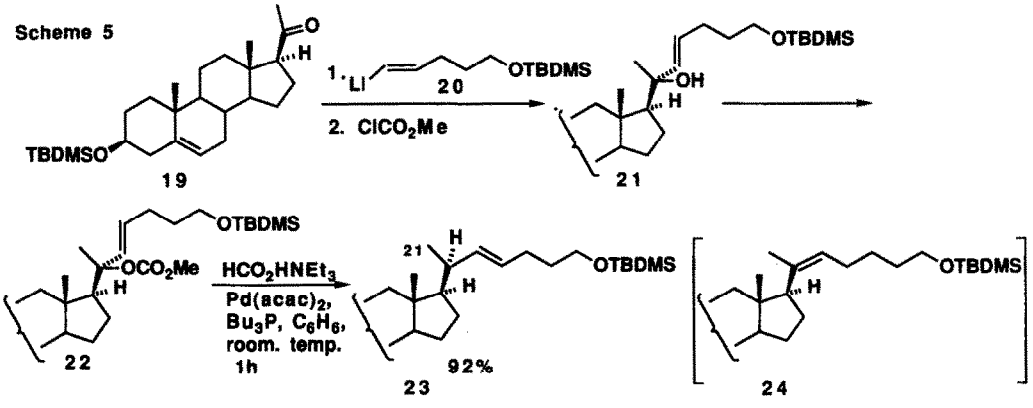
Control of C-20 stereochemistry. So far we have studied the hydrogenolysis of terminal allylic systems to prepare terminal olefins. Then we wanted to extend this regioselective reaction to internal allylic systems **16**. (Scheme 4) "Is the hydrogenolysis of unsymmetrically substituted internal allylic systems **16** regioselective ?" was the question. We expected the formation of **17** by the preferencial hydride attack at the tertiary carbon, rather than the secondary carbon to form **18**.



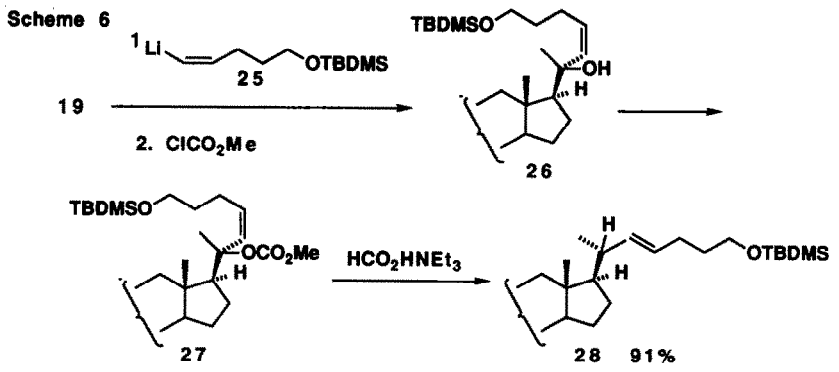
We hoped to apply this regioselective hydrogenolysis to the C-20 allylic carbonate in a steroid side chain, expecting the regioselective formation of the C-22(23) olefin. Namely, in the reaction of the following model compounds of allylic carbonates **22** and **27**, we expected that the hydride would attack the crowded tertiary

carbon to form C-22(23)olefins **23** and **28** without attacking secondary carbon to form C-22(23) olefin **24**. In addition to the regioselectivity, we expected the stereoselectivity based on mechanistic considerations that the displacement of the carbonate group with hydride would take place with net inversion of stereochemistry,[38] so that both C-20 epimers **23** and **28** would be formed stereospecifically from the (E) and (Z)-allylic carbonates **22** and **27**. We were pleased to find that the reactions, in fact, proceeded as expected.[18]

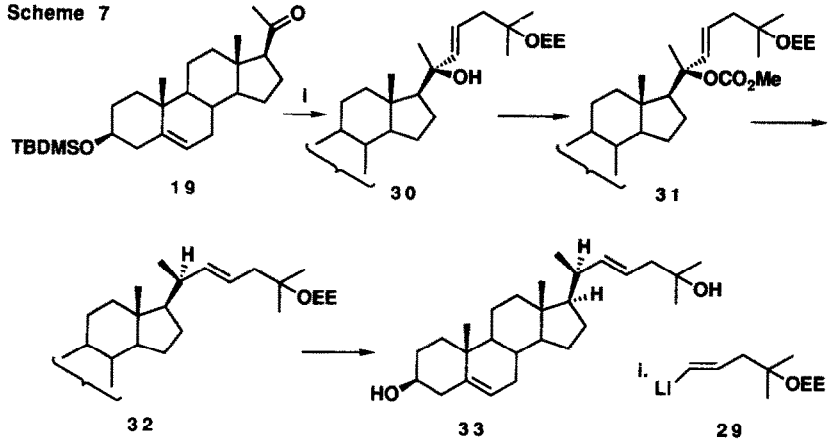
At first, we tried the reaction with model compounds. We prepared both pure (E) and (Z)-steroidal C-20 allylic alcohols **21** and **26** by the reaction of (E) and (Z)- 5-t-butyldimethylsilyloxy-1-pentenyllithium (**20** and **25**) with the C-20 keto steroid **19.** The reaction of **20** and **25** takes place from the α side, and the 20β-allylic alcohols **21** and **26** were obtained as solid after column chromatographic purification. Allylic formate is preferable than carbonate for the hydrogenolysis, but the formate of tertiary allylic alcohol could not be prepared. Thus the allylic alcohols **21** and **26** were converted to the carbonates **22** and **27** which were too unstable to purify. Without purification, the carbonates were subjected to the palladium catalysis. The catalyst solution was prepared by dissolving purified $Pd(acac)_2$ and n-Bu_3P in a 1:1 ratio in benzene. After stirring for five min, an equimolar mixture of triethylamine and formic acid (five equivalents) was added to give a pale yellow solution. Then the (E)-carbonate **22** was added. During the reaction, the initially pale yellow solution turned to dark brown. The reaction proceeded at room temperature to give, regioselectively, the expected C-22(23) olefin in 92% yield. Investigation of the isolated product by TLC and NMR techniques showed the absence of the regioisomeric C-20(22) olefin **24.** (Scheme 5)



Similarly the (Z) carbonate **27** was subjected to the palladium catalysis with an excess of formic acid and triethylamine to give **28** in 91% yield. (Scheme 6) It was confirmed that the isomeric allylic carbonates **22** and **27** gave the different products **23** and **28** in high yields. Their isomeric purity was determined by means of HPLC after desilylation of **23** and **28** and their conversion to the corresponding dibenzoates. This showed that the unnatural C-20 stereochemistry **23** had been created with very high purity (above 99%). On the other hand, the selectivity for the natural isomer **28** was 9 : 100 (**23** : **28**). The ^1H NMR absorption at δ 0.87, assignable to the C-21 CH_3 group in **23** supports the conclusion that the unnatural epimer **23** had been formed from the E isomer **21**. The product **28** obtained from the Z isomer **26** showed the corresponding ^1H NMR absorption at δ 0.98, which is reasonable for a natural epimer.[39]



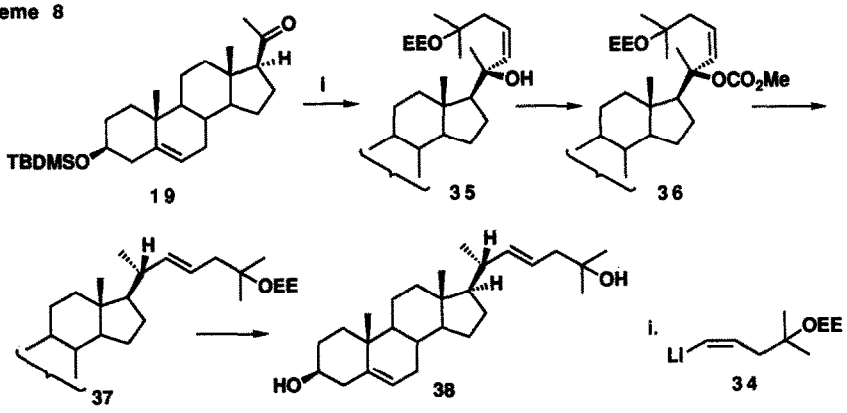
Encouraged by the success of regioselective and stereospecific reaction of the model compounds **22** ans **27**, we prepared the protected (E) and (Z)-4-hydroxy-4-methyl-1-pentenyl iodides as the *cis* and *trans* steroidal side chain units from 4-hydroxy-4-methyl-1-pentynyl iodide as the common intermediate, and their lithium derivatives **29** and **34** were introduced to the C-20 keto steroid **19**. The 20β allylic alcohols **30** and **35** were purified and then converted to the carbonates **31** and **36**. Then the E isomer **31** was treated with five equivalents of the mixture of formic acid and triethylamine. (Scheme **7**) The reaction took 30 min to complete. It was deprotected (pyridinium *p*-toluenesulfonate in MeOH) to give the diols **33** [82% from **30**, mp, 205-205.5°C (needles, recrystallized from benzene), $[\alpha]_D$ = -54.35°, $CHCl_3$].



Similarly the Z isomer **36** was treated with 1.5 equivalents of the reductant for 1.5 h to complete. (Scheme 8) It was deprotected (pyridinium *p*-toluenesulfonate in MeOH) to give the diol **38** [90% from **35**, mp, 180-180.5°C (needles, recrystallized from benzene), 178-178.5°C (needles, from methanol), $[\alpha]_D$ = -51.38°, $CHCl_3$ [40]]. The isomeric allylic carbonates **31** and **36** gave the different products **33** and **38** in high yields. Their isomeric purity was determined by means of HPLC after converting **33** and **38** to the corresponding monobenzoates. The results show that the reaction was regioselective and stereospecific. The unnatural diol **33**

had been formed with very high purity (above 99%). On the other hand, the selectivity for the natural diol **38** was 9 : 100 (**33** : **38**) from **36**. The NMR absorption at δ 0.92, assignable to the C-21 CH_3 group in **33** supports the conclusion that the unnatural epimer had been formed from the E isomer **30**.[39] The product **38** obtained from the Z isomer **35** showed the corresponding NMR absorption at δ 1.03, which is reasonable for a natural epimer. [39]

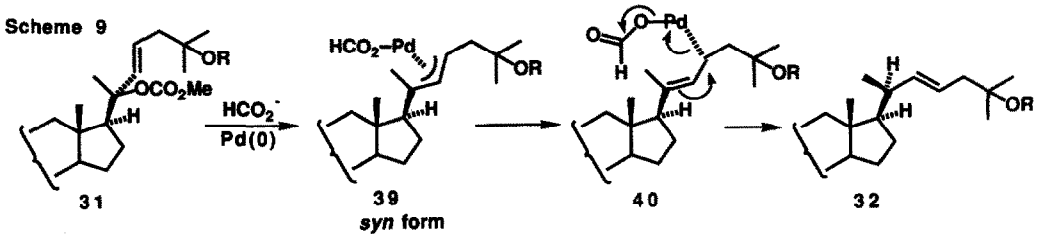
Scheme 8



MECHANISM OF THE REACTION

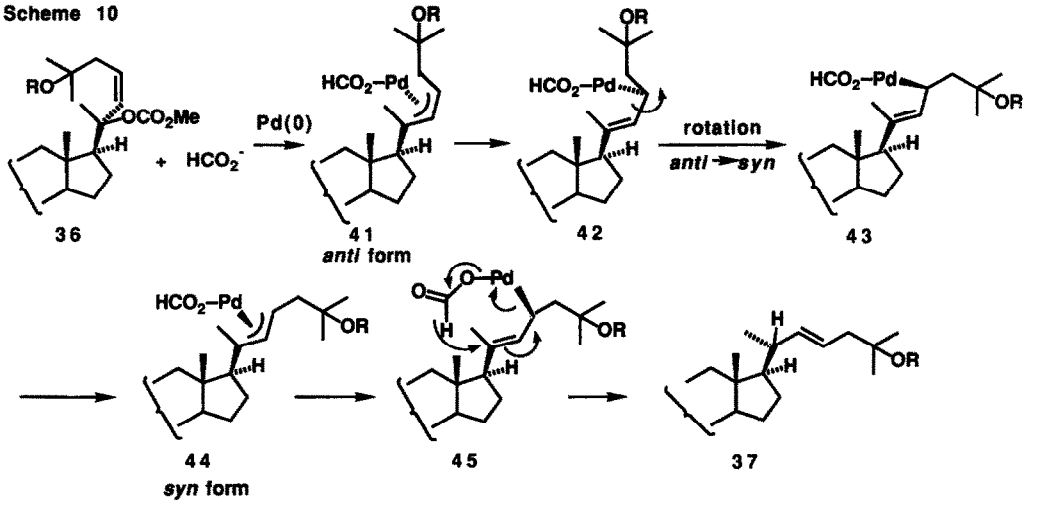
Although we have no direct evidence at present, we wish to propose the following mechanism for these stereospecific reactions. Formation of π-allyl-palladium formate **39** takes place from the E isomer **31** by the attack of Pd(0) from the back side, with inversion, to give an α-oriented palladium species. The complex **39** has a stable *syn* form [41] and the concerted decarboxylation-hydride transfer of **39** takes place from the α-side, with retention, to give the unnatural configuration **32** as shown by **40**. (Scheme **9**)

Scheme 9



On the other hand, the Z isomer **36** affords the π-allylpalladium formate **41**, which has the *anti* form [41] and a large steric repulsion between the methyl and the side chain. Therefore, transformation from the unstable *anti* **41** to the stable *syn* form **44** takes place by rotation of σ-allylpalladium **42** prior to the hydride transfer. At the same time, by this rotation, Pd moves to the β-side **43**, and hence the hydride transfer **45** takes place from the β-side to give the natural configuration **37**. (Scheme **10**) The somewhat lower selectivity observed for the natural isomer **37** is understandable, because the inversion of stereochemistry takes place before the hydride transfer by the external attack of Pd(0) species to give **32** to a small extent.

Scheme 10



PREPARATION OF THE ACTIVE PALLADIUM CATALYST

It should be emphasized that the purity of $Pd(acac)_2$ and n-Bu_3P is critically important for consistent results. Commercially available $Pd(acac)_2$ was recrystallized from benzene (needle-like crystals). n-Bu_3P in a "Sure-Seal" bottle, purchased from Aldrich was used. We observed no or poor conversion when slightly impure n-Bu_3P purchased from other companies was used. $Pd(OAc)_2$ can be used, but $Pd(acac)_2$ gave somewhat better results than $Pd(OAc)_2$. The active catalytic species seems to be Pd(0) formed by the reaction of n-Bu_3P, which is oxidized to phosphine oxide. ^{31}P NMR studies revealed that absorption due to n-Bu_3P disappeared rapidly when $Pd(acac)_2$ and n-Bu_3P were mixed. Thus the active catalyst is phosphine-free Pd(0) weakly coordinated by phosphine oxide.[42] $Pd_2(dba)_3$, which contains Pd(0), was used as a catalyst by mixing with phosphine. However, $Pd_2(dba)_3$ combined with n-Bu_3P was totally inactive in this hydrogenolysis. Possiblly, dba is a strongly coordinating bidentate olefin ligand, and inhibits the coordination of somewhat hindered olefins of the substrates. Recently, studies on the reduction of $Pd(OAc)_2$ to Pd(0) species with phosphine was reported.[43, 44]

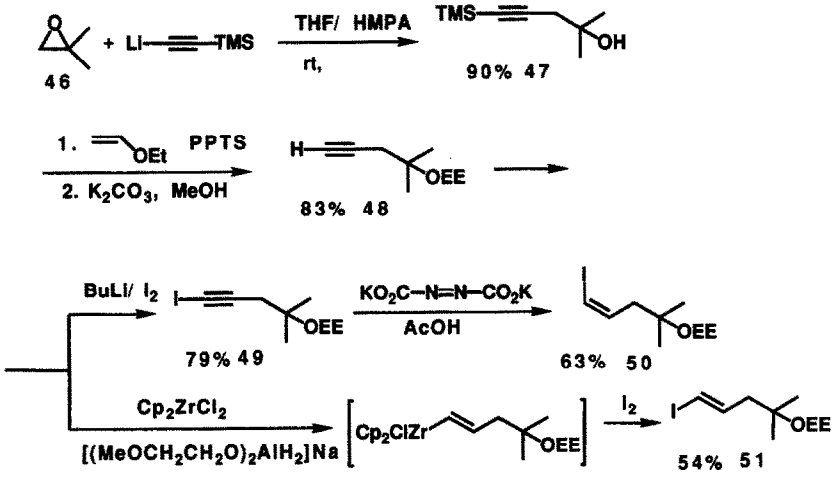
$$Pd(acac)_2 + Bu_3P \longrightarrow Pd(0) \cdots O{=}PBu_3$$

CONCLUSION

The method described in this paper offers a convenient preparative method for the natural and unnatural C-20 epimers of steroids from easily available C-20 keto steroids as a common starting material. In addition, the *cis* and *trans* side chain units can be prepared from the same acetylenic compound **48** by the following sequence of reactions. (Scheme **11**)

This novel method suggests that the palladium-catalyzed regio- and stereospecific hydrogenolysis of allylic carbonates with formate should become a powerful synthetic tool.

Scheme 11



EXPERIMENTAL SECTION

General method. The 400 MHz ^{1}H and 100 MHz ^{13}C NMR spectra were recorded on a JEOL GX-400 instrument. Deuteriochloroform was used as a solvent, where the chemical shifts are given in δ units relative to internal $CHCl_3$. Analytical TLC was measured on pre-coated Merck silica gel 60 F254 (0.25 mm thickness). Column chromatography was performed on silica gel (230-400 mesh).

The purity and ratio of the epimers were determined as the monobenzoates by HPLC. The retention times for 3-benzoates of **33** and **38** were 7.76 and 8.31 min. (Develosil 30-3, 4.6 mm x 250 mm, hexane-ethyl acetate (3:1)).

Materials. Commercially available $Pd(acac)_2$ was recrystallized from benzene (needle-like crystals). n-Bu_3P was purchased from Aldrich in a "Sure-Seal" bottle.

1. Preparation of C-17β-isopropenyl steroid 11. The carbonate **10** (251 mg, 0.5 mmol), prepared from androsterone **9** by the reaction with isopropenyllithium and subsequently with methyl chloroformate by a similar method as applied to **31**, was treated with a mixture of $Pd(acac)_2$ (30.4 mg,0.1mmol) and Bu_3P(0.024 ml, 0.1 mmol) in the presence of a mixture of HCO_2H and Et_3N (2.5 mmol) in THF at room temperature for 3 h. and 17β-isopropenyl stroid **11** was obtained in 83% yield (178 mg). The structure was determined by comparison of its ^{1}H NMR and ^{13}C NMR spectra with those of an authentic sample prepared by Wittig reaction of C-20 keto steroid. Both spectra were completely identical.

2. Preparation of C-17β-(3-isobutenyl) steroid 14 from the C-23 formate 13. The formate **13** (229 mg, 0.47 mmol) was treated with $Pd(acac)_2$ and Bu_3P (20 mol% each) in benzene at room temperature for 3 h. The conclusion that the product **14** (197 mg) is a 1:1 mixture of the C-20 epimers was supported by the

following ^{1}H NMR spectral data. Two singlet peaks for the C-18 methyl with identical integration were observed at δ = 0.66 and 0.70. Also two doublets for the C-21 methyl were observed at δ = 0.91 (d, J = 6.65) and 1.03 (d, J = 6.65).

3. Preparation of the unnatural epimer 33

Preparation of allylic alcohol 30; The *trans* alkenyl iodide (1.28 g, 4.3 mmol) was treated with t-BuLi (8.6 mmol) in ether (10 mL) at -80°C and the mixture was stirred for 1 h to form **29**. To this solution, the 17-keto steroid **19** (1.29 g, 3 mmol) in THF (15mL) was added slowly and the mixture was stirred at -80°C for 20 min and warmed to room temperature in 40 min. The reaction mixture was quenched with water and extracted with ethyl acetate. After the usual work-up, a crude product was obtained as a solid, which was purified by SiO_2 gel column chromatography to give the allylic alcohol **30** as solid. (789 mg, 44 %). A considerable amount of the keto steroid **19** was recovered.

Preparation of the carbonate; A solution of n-BuLi (1.0 mL, 1.57 mmol) was added dropwise in 5 min at -80°C to THF solution of the allylic alcohol **30** (789 mg, 1.31 mmol). The mixture was stirred for 30 min, and methyl chloroformate (0.15 mL, 1.97 mmol) was added at -80°C, and the solution was stirred for 3 h. After being warmed to room temperature, the reaction was quenched with aqueous $NaHCO_3$ and extracted with ethyl acetate and dried ($MgSO_4$). A crude carbonate **31** was obtained as an oil after evaporation of the solvent and used in the next step without purification..

Hydrogenolysis; $Pd(acac)_2$ (79.6 mg, 0.26 mmol) and n-Bu_3P (0.065 mL, 0.26 mmol) were mixed in benzene (2 mL) and the mixture was stirred at room temperature for 5 min. A mixture of HCO_2H and Et_3N (6.5 mmol each) was added to afford a pale yellow solution. Then the carbonate **31** obtained in the above and dissolved in benzene (2 mL) was added and the mixture was stirred at room temperature for 45 min. TLC analysis of the reaction mixture showed the disappearance of the carbonate in 30 min. Benzene (50 mL) was added, and the mixture was washed with water. The dried solution was evaporated to give **32** as an oil. Deprotection of **32** using pyridinium *p*-toluenesulfonate in MeOH afforded the diol **33.** 430 mg, 82% from **30**, mp, 205-205.5°C (needles, recrystallized from benzene), $[\alpha]_D$ = -54.35° (c = 0.471, $CHCl_3$), Anal. Calcd for $C_{27}H_{44}O_2$: C, 80.94; H, 11.07. Found: C, 80.93; H, 11.46.

^{1}H NMR δ, 0.66 (s, 3H, CH_3 (C-18)), 0.92 (d, J = 6.60 Hz, 3H, CH_3 (C-21), 0.99 (s, 3H, CH_3 (C-19)), 1.201, 1.204 (s, 3H, CH_3 (C-26, 27)), 3.46-3.55 (m, 1H, OCH), 5.31-5.46 (m, 3H, C=CH). ^{13}C NMR, δ, 12.1, 19.4, 20.8, 21.7, 24.1, 27.9, 31.7, 31.8, 31.9, 36.5, 37.2, 39.2, 40.4, 42.3, 42.4, 47.0, 50.2, 56.1, 56.6, 70.7, 71.8, 121.6, 122.5, 140.8, 141.9.

4. Preparation of the natural epimer 38

The *cis* allylic alcohol **35** was prepared similarly from C-17 keto steroid **19** in 77.7% yield. The carbonate **36**, prepared from the allylic alcohol **35** (634 mg, 1.05 mmol), was used without purification for the hydrogenolysis using $Pd(acac)_2$ (64 mg, 0.21 mmol), n-Bu_3P (0.052 mL, 0.21 mmol), a mixture of HCO_2H and Et_3N (2.1 mmol each) in benzene (5 mL) at room temperature for 1.5 h to give crude **37** as an oil. The crude product was deprotected with pyridinium *p*-toluenesulfonate to afford the diol **38** as a solid. [376 mg, 90 % from **35**, mp, 180-180.5°C (needles, recrystallized from benzene), 178-178.5°C (needles, from MeOH). $[\alpha]_D$ = -51.38°, (c = 0.253, $CHCl_3$) The different mp 168-171°C (recrystallized from MeOH), and $[\alpha]_D$ = -50.8° (no solvent was reported) were reported.[40]

^{1}H NMR, δ, 0.70 (s, 3H, CH_3 (C-18)), 1.00 (s, 3H, CH_3 (C-19)), 1.03 (d, J = 6.59 Hz, 3H, CH_3 (C-21)), 1.19 (s, 6H, $2CH_3$ (C-26, 27)), 3.46-3.57 (m, 1H, OCH), 5.31-5.43 (m, 3H, C=CH). ^{13}C NMR ($CDCl_3$), δ, 12.1, 19.4, 20.7, 21.1, 24.3, 28.8, 29.0, 31.6, 31.9, 36.5, 37.2, 39.7, 40.3, 42.3, 46.8, 50.1, 55.6, 56.8, 70.5, 71.8, 121.6, 122.5, 140.7, 141.9.

The diol **38** was converted to the monoacetate. mp, 140-141°C, Anal Calcd for $C_{29}H_{46}O_3$: C, 78.68; H, 10.47. Found: C, 78.75; H, 10.72.

^{1}H NMR, δ, 0.69 (s, 3 H, CH_3 (C-18)), 1.01 (s, 3H, CH_3(C-19)), 1.03 (d, J = 6.60 Hz, 3H, CH_3 (C-21)), 1.19 (s, 6H, $2CH_3$ (C-26, 27)), 2.02 (s, 3H, $COCH_3$), 4.55-4.64 (m, 1H, C-3 proton), 5.82-5.92 (m, 3H, C=CH). ^{13}C NMR , δ, 12.0, 19.3, 20.7, 21.0, 21.4, 24.3, 27.7, 28.8, 29.0, 31.8 (overlap), 36.6, 37.0, 38.1, 39.6, 40.3, 42.3, 46.8, 50.0, 55.6, 56.7, 70.5, 73.9, 122.5, 122.6, 139.6, 141.8, 170.5.

5. Preparation of 23

Preparation of allylic carbonate 22. To an ethereal solution of t-BuLi (4.7 ml, 7.0 mmol) was added (E)-5-t-butyldimethylsilyloxy-1-iodo-1-pentene (1.233g, 3.67 mmol) in 15 min at -83°C to form **20.** Then a solution of 17-keto steroid **19** (860 mg, 2.0 mmol) in THF (13 ml) was added, and the mixture was stirred for 1.5 h at -83°C. The reaction was quenched with water and extracted with ethyl acetate. The organic layer was washed with water, dried ($MgSO_4$), and evaporated to give a pale yellow solid (1.65 g), and purified by column chromatography on silica gel to give the allylic alcohol **21** as white crystals (939 mg, 74.5%).

To THF (8ml) solution of the allylic alcohol (939 mg) was added t-BuLi (1.2 ml, 1.79 mmol) at -83°C over 5 min. The mixture was stirred for 30 min. Methyl chloroformate (0.17 ml, 2.24 mmol) was added dropwise and the reaction mixture was stirred for 14 h at -83°C. The mixture was quenched with aqueous $NaHCO_3$ and extracted with ethyl acetate. The organic layer was washed with aq. $NaHCO_3$ and dried ($MgSO_4$). The carbonate **22** was obtained as a colorless oil after evaporation of the solvent (992.5 mg).

Hydrogenolysis. The catalyst solution was prepared by dissolving $Pd(acac)_2$ (30.4 mg, 0.1 mmol) and n-Bu_3P (0.025 ml, 0.1 mmol) in benzene (2 ml) at room temperature to give a pale yellow solution. Then an equimolar mixture of HCO_2H and Et_3N (5 ml, 5 mmol) was added, followed by the addition of the crude carbonate **22** (688mg, 1.0 mmol) in benzene (9ml). The reaction mixrture was stirred at room temperature for 3 h. Hexane (40 ml) was added to the reaction mixture and the organic layer was washed with water and dried ($MgSO_4$). The olefin **23** (568.7 mg, 92%) was obtained as solid after evaporation of the solvent. ^{1}H NMR, δ 0.87 (C-21 Me)

6. Preparation of 28

Preparation of (Z)-carbonate 27. The allylic alcohol **26** was prepared similarly. (Z)-5-t-Butyldimethylsiloxy-1-iodo-1-pentene (2.65 g, 8.1 mmol) was treated with t-BuLi (10.2 ml, 15.4 mmol) in ether to form **25**, and 17-keto steroid **19** (1.74 g, 4.05 mmol) was added. Crude allylic alcohol **26** (3.44 g) was obtained as a brown oil, which was purified to give the allylic alcohol **26** (3.37 g) as brown oil.

The allylic alcohol (513 mg, 0.815 mmol) was converted to the carbonate **27** by the treatment with t-BuLi (0.65 ml, 0.978 mmol) and methyl chloroformate (0.094 ml, 1.223 mmol) for 16 h. The carbonate **27** (539 mg) was obtained as a white solid.

Hydrogenolysis. The carbonate **27** (539 mg,1.29 mmol) was treated with $Pd(acac)_2$ (30.4 mg, 0.1 mmol), n-Bu_3P (0.025ml, 0.1 mmol) and an equimolar mixture of HCO_2H and Et_3N (7.8 ml, 7.8 mmol) in benzene at room temperature for 1.5 h. After the ususal work-up, the olefin **28** (435.9 mg, 91%) was obtained as a yellow solid. ^{1}H NMR, δ 0.98 (C-21 Me)

7. Preparation of the protected *cis* and *trans* side chain units. a) (E)-4-hydroxy-4-methyl-1-pentenyl iodides (51) (Scheme **11**) To TMS acetylene (5.64 ml, 40 mmol) in THF (30 ml) was added n-BuLi (26.9 ml, 42 mmol) at 0°C. After stirring 35 min, HMPA (7 ml) and isobutylene oxide **46** (3.96 ml, 44 mmol) was added, and the mxture was stirred at room temperature for 20 h. After the usual workup, the alcohol **47** was obtained in 89.9% (6.1 g). The alcohol was protected as 1-ethoxyethyl ether, and the product was desilylated with K_2CO_3 in MeOH to give **48** as a colorless oil (2.1 g, 82.5%). To a THF(40 m) solution of Cp_2ZrCl_2 (4.32 g, 14.8 mmol) was added Vitride $[(MeOCH_2CH_2O)_2AlH_2]Na$ (20.3 ml, 6.7 mmol) at room temperature over 50 min. Then the solution of **48** (2.1 g, 12.3 mmol) in benzene (15 ml) was added dropwise over 30 min, and the mixture was stirred for 75 min. The solution of I_2 (4.7 g, 18.5 ml) in THF (10 ml) was added and the mixture was stirred for 50 min. The reaction was quenched with $Na_2S_2O_3$ and the product was extracted with a mixture of benzene and ethyl acetate. After the usual workup, the crude product was purified by column chromatography (silica gel, hexane-ethyl acetate 15:1) to give (E)-iodide **51** as a light yellow oil (1.98 g, 54%). ^1H NMR, δ, 6.60 (dt, J = 14.3, 7.70 Hz, 1H, I-C=CH), 6.11 (d, J = 14.3 Hz, 1H, I-CH=C)

b) (Z)-4-hydroxy-4-methyl-1-pentenyl iodides] (50) The protected acetylenic alcohol **48** (1.642 g, 9.65 mmol) in THF (10 ml) was treated with n-BuLi (7.4 ml, 11.59 mmol) at -78°C for 15 min, and I_2 (3.19 g, 12.56 mmol) in THF (5 ml) was added. After the usual workup, the iodoacetylene **49** was obtained in 79% yield (2.257 g) as light yellow oil. To a MeOH(35 ml) solution of **49** (2.257 g, 7.62 mmol) and potassium azodicarboxylate (7.391 g, 38.1 mmol), AcOH (7.84 ml, 137 mmol) was added dropwise in 1.5 h at room temperaure, and the mixture was stirred for 2.5 h. The reaction was quenched with 3N-NaOH and the mixtuire was extracted with hexane. An oily crude product was purified by column chromatography to give (Z)-vinyl iodide **50** in 63% yield (1.1429 g). ^1H NMR, δ, 6.33 (d, J = 7.7 Hz, 1H, I-CH=C), 6.30 (dt, J = 7.70, 5.50 Hz, 1H, I-C=CH)

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(*Received* 24 *May* 1993)