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

Tadakatsu Mandai,* Takaji Matsumoto, Mikio Kawada, and Jiro Tsuji*

Department of Applied Chemistry, Okayama University of Science, Ridai-cho, Okayama, Japan 700

Received July 31, 1992

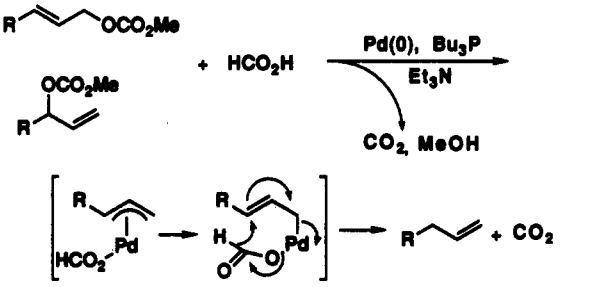
Summary: Both natural and unnatural epimers at C-20 in a steroid side chain can be generated stereospecifically by the palladium-catalyzed hydrogenolysis with triethylammonium formate of C-20 (*Z*) or (*E*) allylic carbonates, respectively.

One important problem in the total or partial synthesis of steroids is creation of the correct natural configuration at C-20 in a side chain. Several stereoselective methods for introducing the side chains of the natural configuration in the steroid skeleton have been reported.[1-15] 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 those 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.

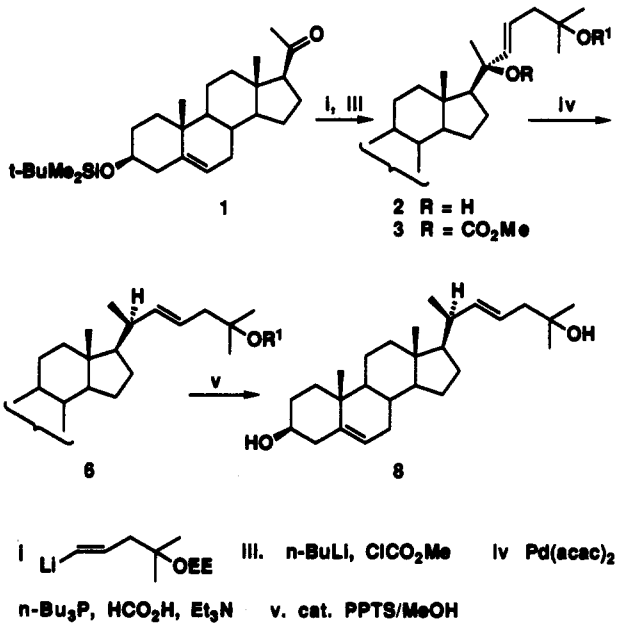
In this paper, we wish to report a simple new method for creating either the natural or unnatural configuration at C-20, at will. The method is based on the palladium-catalyzed hydrogenolysis of C-20 (*E*) and (*Z*) allylic carbonates with formic acid. We have reported that the palladium-catalyzed hydrogenolysis of allylic compounds, particularly carbonates, with triethylammonium formate affords olefins with high regioselectivity.[17] The most important feature of this reaction is that the hydride generated from formate attacks regioselectively the more substituted side of the allylic system. (Scheme I) 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.[18]

We hoped to apply this regio- and stereoselective hydrogenolysis to the C-20 allylic carbonate, expecting the regioselective formation of the C-22(23) olefin. In addition, we expected, based on mechanistic considerations that the displacement of the carbonate group with hydride would take place with net inversion of stereochemistry, that both C-20 epimers would be formed stereospecifically from the (*E*) and (*Z*) allylic carbonates **3** and **5**. We were pleased

Scheme I



Scheme II



(1) A number of methods for stereocontrolled construction of C-20 stereochemistry have been reported: (a) ene reaction of 17(*E*)-ethylidene derivatives with acrylate[2a] and propiolate;[2b,3] (b) reactions via 16-hydroxy-17(*E*)-ethylidene derivatives, Wittig rearrangement,[4,5] 3,3-Claisen rearrangement,[6] Carroll rearrangement,[7] and oxy-Cope rearrangement;[8] (c) stoichiometric and catalytic reactions of π-allylpalladium complexes with soft carbon nucleophiles[9,10] and hard carbon nucleophiles;[11] (d) reactions via organocopper reagents;[12,13] (e) the stereospecific alkylation of 21-oic acid esters, the ester group being a precursor of methyl group;[14] and (f) stereospecific hydroboration of 20(22) methylene steroids with hindered boranes.[15]

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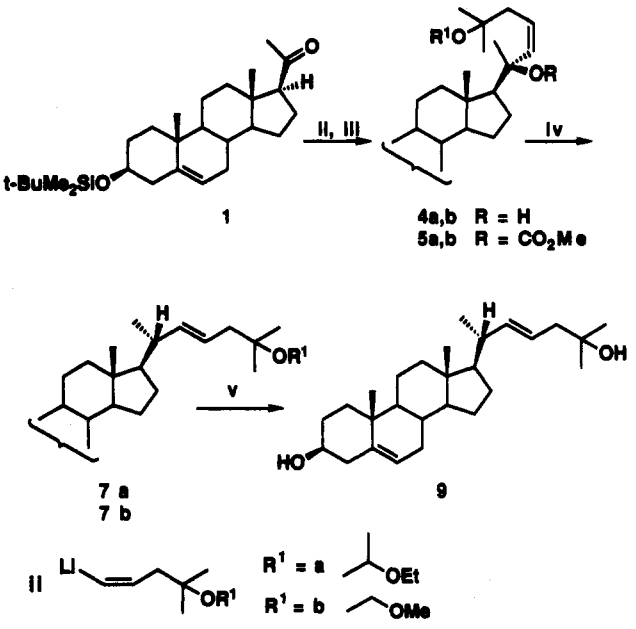
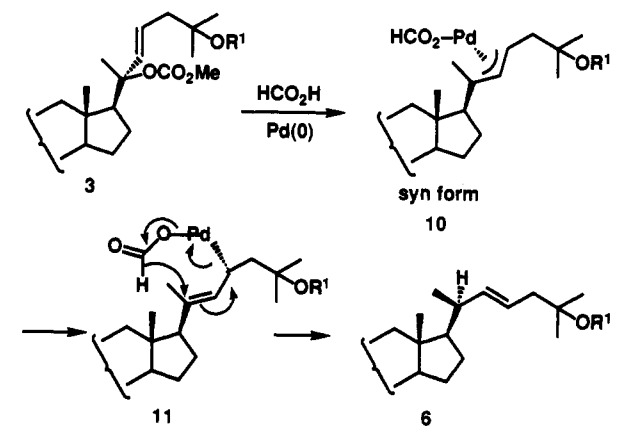
Scheme III



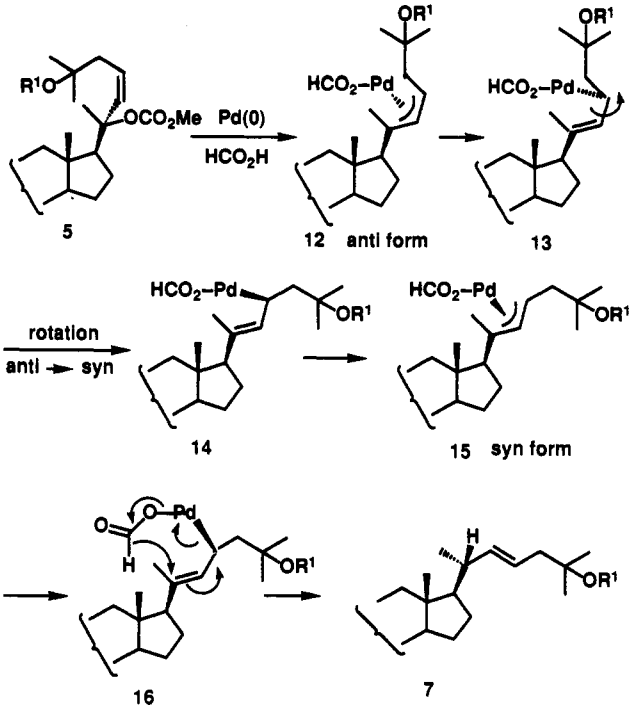
Scheme IV



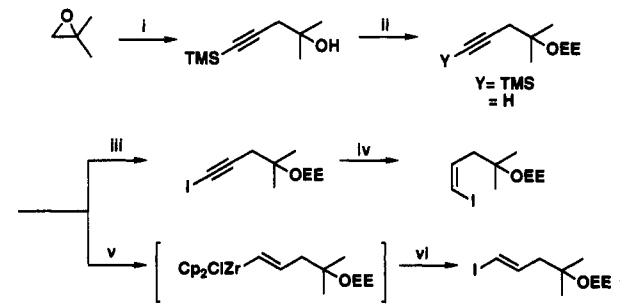
to find that the reactions, in fact, proceeded as expected.

Both pure (*E*) and (*Z*) steroidal C-20 allylic alcohols **2** and **4a,b** were prepared from the C-20 keto steroid **1** and converted to the carbonates **3** and **5a,b** which, without purification, were treated with an excess of triethylamine and formic acid (1:1 mixture; 5 equiv were used for **3** and 2 equiv for **5a,b**) in the presence of a catalyst prepared from $Pd(acac)_2$ and n-Bu_3P (1:1)[19] in THF (Schemes II and III). The pale yellow solution of the catalyst turned to dark brown. The reaction proceeded rapidly at room temperature to give, regioselectively, the expected C-22(23) olefins. The reaction took 30 min for **3** and 1.5 h for **5a** and **5b** to complete. The regioisomeric C-20(22) olefin was not detected. Furthermore, the isomeric allylic carbonates **3** and **5a,b** gave the different products **6** and **7a,b** in high yields. They were deprotected (pyridinium *p*-toluenesulfonate in MeOH) to give the diols **8** [82% from **2**, mp 205–205.5 °C (needles, recrystallized from benzene), $[\alpha]_D$ = –54.35°, $CHCl_3$] and **9** [92% from **4a** and 90% from **4b**,

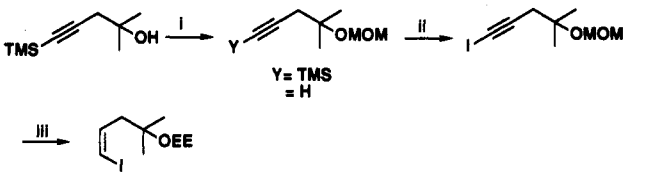
Scheme V



Scheme VI



i) Li—≡—TMS THF/HMPA, r.t., 21 h, 90% ii) ethyl vinyl ether, cat. PPTS, CH_2Cl_2, r.t., 5 h, then, K_2CO_3/MeOH, r.t., 1.5 h, 83% iii) n-BuLi, THF, I_2, -78 °C, 1 h, 79% iv) KO_2C-N=N-CO_2K, AcOH/MeOH, r.t., 2.5 h, 63% v) Cp_2ZrCl_2, $[(MeOCH_2CH_2O)_2AlH_2]Na$, THF/PhH, r.t., 1.5 h vi) I_2, THF, r.t., 1 h, 54%



i) $ClCH_2OMe$, iPr_2EtN, CH_2Cl_2, r.t., 14 h, then, K_2CO_3/MeOH, r.t., 1 h, 70% ii) n-BuLi, THF, I_2, -78 °C, 1 h, 95% iii) KO_2C-N=N-CO_2K, AcOH, MeOH, r.t., 2.5 h, 92%

mp 180–180.5 °C (needles, recrystallized from benzene), 178–178.5 °C (needles, from methanol), $[\alpha]_D$ = –51.38°, $CHCl_3$[20]]. Their isomeric purity was determined by means of HPLC after converting **8** and **9** to the corresponding monobenzoates. This showed that the unnatural diol **8** had

(19) 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. No reaction or poor conversion was observed with slightly impure n-Bu_3P purchased from other companies.

(20) The mp 168–171 °C (recrystallized from methanol) and $[\alpha]_D$ = –50.8° of the compound **9** were reported. Moiseenkov, A. M.; Ceskis, B. A.; Semenovskii, A. V.; Bogoslovskii, N. A.; Litvinova, G. E.; Samokhvalov, G. I.; Segal, A. G.; Torgov, I. V. *Bioorg. Khim.* **1983**, *9*, 118; *Chem. Abstr.* **1983**, *98*, 198577h.

been formed with very high purity (above 99%). On the other hand, the selectivities for the natural diol **9** were 9:100 (**8**:**9**) from **4a** and 6:100 from **4b**.[21] The NMR absorption at δ 0.92, assignable to the C-21 CH_3 group in **8**, supports the conclusion that the unnatural epimer had been formed from the (*E*) isomer **2**. The product **9** obtained from the (*Z*) isomer **4a,b** showed the corresponding NMR absorption at δ 1.03, which is reasonable for a natural epimer.[22]

These stereospecific reactions can be understood by the following mechanism. Formation of π-allylpalladium formate **10** takes place from the (*E*) isomer **3** by the attack of Pd(0) from the bottom side, with inversion, to give an α-oriented palladium species. The complex **10** has a stable syn form,[23] and the concerted decarboxylation–hydride transfer of **11** takes place from the α-side, with retention, to give the unnatural configuration **6** (Scheme IV). On the other hand, the (*Z*) isomer **5** affords the π-allylpalladium formate **12**, which has the anti form[23] and a large steric repulsion between the methyl and the side chain. Therefore, transformation from the unstable anti **12** to the stable syn form **15** takes place by rotation of σ-allylpalladium **13** prior to the hydride transfer **16**. At the same time, by this rotation, Pd moves to the β-side **14**, and hence the hydride transfer **16** takes place from the β-side to give the natural configuration **7** (Scheme V). The somewhat lower selectivity observed for the natural isomer **7** is understandable because the hydride transfer from the α-side takes place to give **6** to a small extent before the rotation (**13** → **14**).

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

Supplementary Material Available: Experimental procedures for main steps and compound characterization data (6 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

(21) The unnatural isomer **8** as the minor product from **5a** was isolated by increasing the ratio of **8**:**9** to 2:8 using 5 equiv of HCO_2H and Et_3N instead of 2 equiv and identified by its NMR spectrum and LC retention time with **8** obtained from **3**.

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(24) The cis and trans side-chain units [protected (*E*)- and (*Z*)-4-hydroxy-4-methyl-1-pentenyl iodides] were prepared by the procedure shown in Scheme VI.

Synthesis of Carbon-Linked Glycopeptides as Stable Glycopeptide Models

Carolyn R. Bertozzi, Paul D. Hoeprich, Jr.,† and Mark D. Bednarski*

Department of Chemistry, University of California, Berkeley, California 94720, and Applied Biosystems, 850 Lincoln Centre Drive, Foster City, California 94404

Received July 22, 1992

Summary: A *C*-glycosyl analog of β-Gal-*O*-Ser has been synthesized and incorporated by automated solid-phase peptide synthesis into a hydrolytically stable, α-helical *C*-glycopeptide.

Protein glycosylation plays a decisive role in intercellular recognition phenomena such as tumor cell metastasis,[1] viral adhesion and infection,[2] and leukocyte trafficking.[3,4] Oxygen-linked glycopeptides in particular have been implicated in the resistance of the proteins to proteolytic degradation[5] and the introduction of conformational restraints on the peptide backbone.[6] The potential of glycopeptides as therapeutic agents has attracted much attention in recent years due to reports of dramatic changes in the activity, stability, and metabolism of glycosylated peptide drugs.[7]

The construction of O-linked glycopeptides by the assembly of glycosylated amino acids presents a challenge to the synthetic chemist due to the sensitivity of the glycosidic bond to the acidic and basic conditions which are used in both solution and solid-phase peptide synthesis.[8] This problem has been addressed by the development of new protecting groups and solid-phase supports that can be cleaved under mild conditions.[9-11] However, O-linked glycopeptides are also subject to both chemical and enzymatic deglycosylation in vivo, an inherent limitation of these materials as potential drugs.

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