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Enantioselective synthesis of (8*S*,13*S*,14*R*)-7-oxa-estra-4,9-diene-3,17-dione

Fu-An Kang,* Nareshkumar Jain and Zhihua Sui

Johnson & Johnson Pharmaceutical Research and Development, LLC, 665 Stockton Drive, Exton, PA 19341, United States

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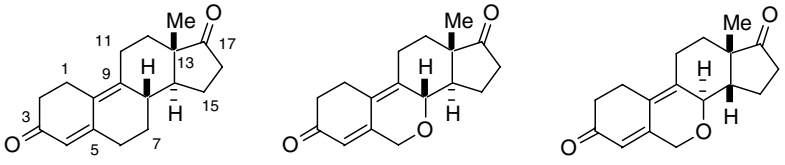
Dedicated to Professor Yoshito Kishi on the occasion of his 70th birthday

Abstract—The first enantioselective synthesis of (8*S*,13*S*,14*R*)-7-oxa-estra-4,9-diene-3,17-dione with the *trans*-C/D ring junction is described. Key features of the synthesis include Ag_2O-mediated C–O bond formation, thermodynamically controlled axial–equatorial inversion, one-pot of halogen exchange and Co/Cr-mediated C–C bond formation, and intramolecular aldol condensations.

In the study of steroid hormones, the naturally occurring steroid core structures have been modified by the insertion of heteroatoms at various positions. Such modifications should mostly retain the shape of the molecules, and could be useful in the identification of novel biologically active molecules and the elucidation of the mechanism of their biological actions. Some of such molecules have exhibited interesting biological activities.[1] Estra-4,9-diene-3,17-dione **1** is known to be an important intermediate to many biologically active steroidal compounds (Fig. 1).[2] Its oxygenated counterpart, 7-oxa-estra-4,9-diene-3,17-dione **2**, is potentially an interesting template that may lead to a series of novel unnatural biologically active substances.

Although compound **2** has not been described in the literature, its reduction product, 17-hydroxy-7-oxa-estra-4,9-diene-3-one, appeared in 1975, which was prepared in 10 steps in 0.35% overall yield.[3] There were three outstanding features of this publication. Firstly, it was not an asymmetric synthesis; instead it relied on chiral resolution of an intermediate with (+)-yohimbine. Secondly, the stereochemistry of the *trans*-fused ring junction, claimed to result from catalytic hydrogenation of an indene derivative, was not clearly confirmed and the structure was not fully characterized. Thirdly, it was disclosed that the advanced compounds derived from this oxa-steroid were found to be biologically inactive toward steroid receptors, and it was further concluded that 'insertion of an oxygen atom into the steroid backbone in place of the 7-methylene group has practically abolished the biological properties of this type of compounds'.[3] As part of our interest in developing novel steroidal compounds as modulators of steroid receptors, we were interested in developing novel oxa-steroidal compounds derived from *trans*-oxa-steroid **2** and



trans-steroid **1** *trans*-oxa-steroid **2** *cis*-oxa-steroid **3**

Figure 1.

* Corresponding author. Tel.: +1 610 458 4147; fax: +1 610 458 8249; e-mail: fkang@prdus.jnj.com

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cis-oxa-steroid **3**. Herein we report the first enantioselective synthesis of compound **2** with the unambiguous *trans*-C/D ring junction.

In the previous letter,[4] we described the first stereoselective synthesis of *rac*-(8*R*,13*S*,14*S*)-7-oxa-estra-4,9-diene-3,17-dione, *cis*-oxa-steroid **3**. We found that catalytic hydrogenation of indenes **4** resulted in the corresponding *cis*-indanes **5** (Fig. 2), which was in contrast to the reports[5] that catalytic hydrogenation of indenes with a large substituent at the C-2 position and a bulky β-oriented protective group at the C-6 position led to *trans*-indanes. During our study on the synthesis of compound **2**, a number of methodologies for the *trans*-indane synthesis were applied to the sterically hindered tetra-substituted indenes **4** for the synthesis of *trans*-indanes **6**, including α-hydroxy directed homogenous catalytic hydrogenation,[6] Cu–Al hydride[7] reduction, and Ni–B hydride[8] reduction. However, these conditions resulted in either recovery of the starting materials or reduction of the carbonyl groups, with the enone system remaining intact in all cases.

In order to construct compound **2** with the unambiguous *trans*-fused ring junction, our new synthesis started with bromide **7**, a known *trans*-indane prepared via stereoselective reductive bromination of the Hajos–Parrish ketone.[9] With the key stereochemistry issue being addressed, the rest of the synthesis seemed to be straightforward, namely, coupling of bromide **7** with a suitable side chain to form ether **8** (Scheme 1) and two intramolecular aldol condensations to construct the molecule. However, it was soon found out that the subsequent key bond formations along this line were not trivial. The key C–O bond formation was the first challenge. O-Alkylation of long-chain alcohols **11a** or **11b** with bromide **7** under various conditions failed to provide the corresponding ethers **8**. Then, O-alkylation of short-chain alcohols with bromide **7** was investigated. A number of two-carbon alcohols and allyl alcohols

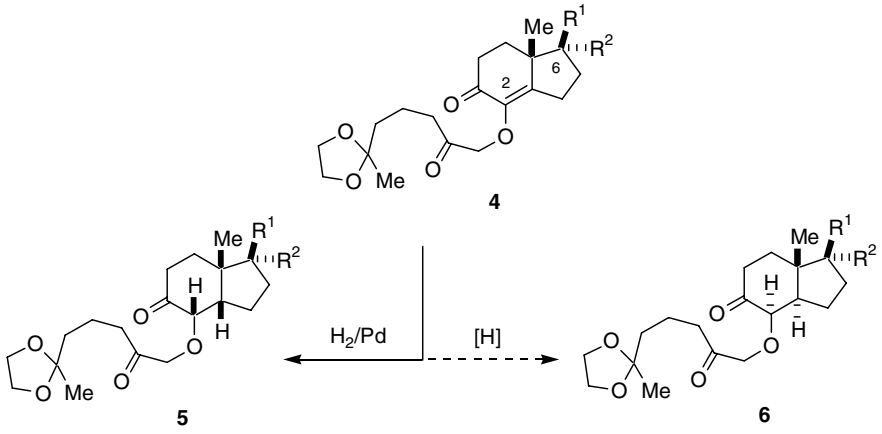
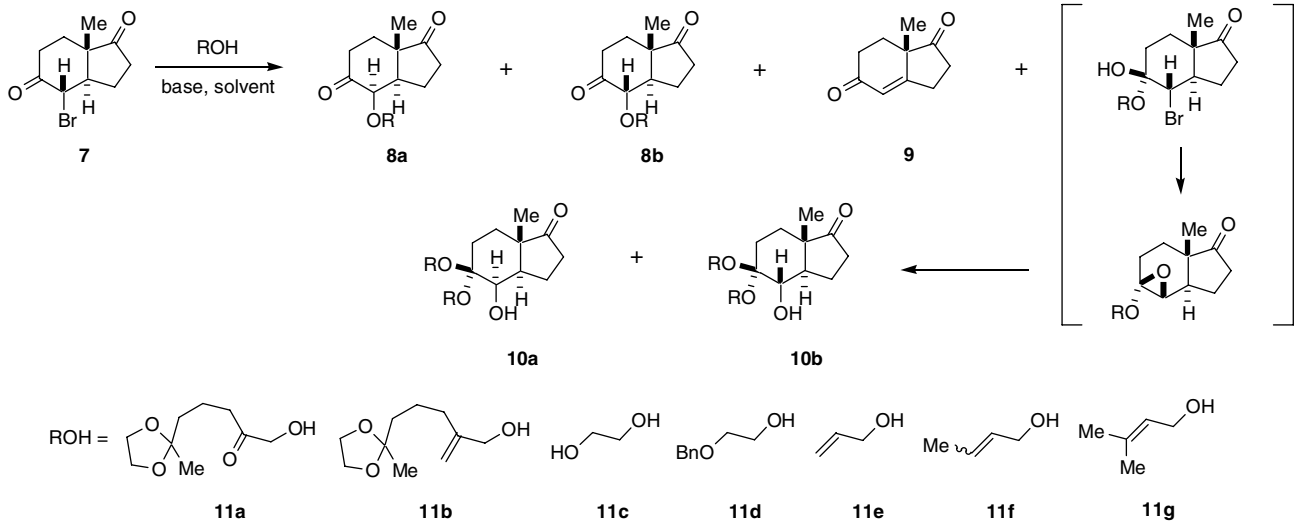


Figure 2. Compound **4a**: $R^1 = R^2 = O$; **4b**: $R^1 = OH$, $R^2 = H$; **4c**: $R^1 = H$, $R^2 = OH$; **4d–f**: $R^1 = OTHP$, OTBS, OPiv, $R^2 = H$.

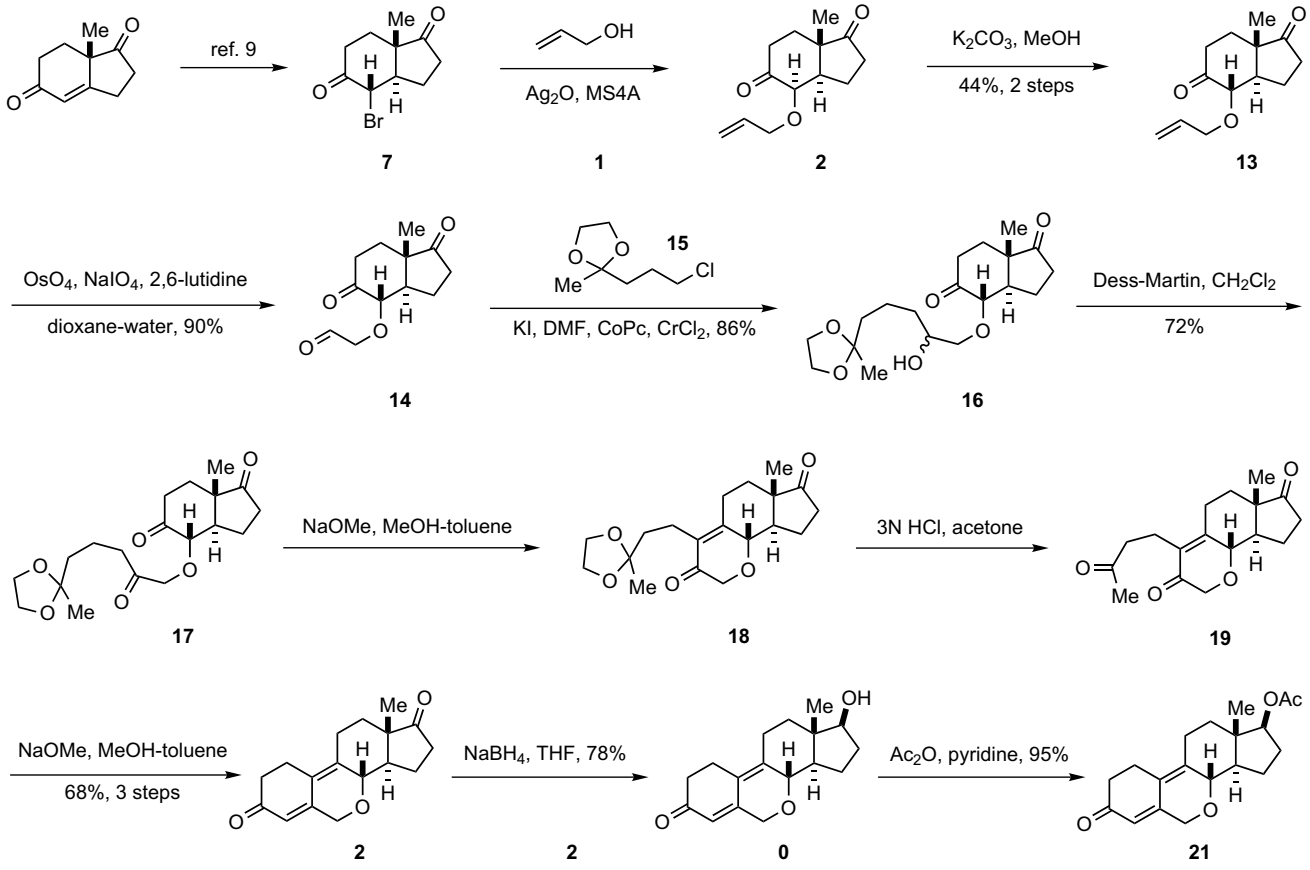


Scheme 1. The following conditions have been screened for the optimal O-alkylation: bases: Cs_2CO_3, K_2CO_3, Na_2CO_3, Li_2CO_3, Cu_2O, Ag_2O, KO*t*-Bu, NaH; solvents: hexane, cyclohexane, CH_2Cl_2, Et_2O, THF, DME, dioxane, DMF, benzene, toluene, xylenes, cumene, trifluoromethylbenzene; temperatures: −40 °C, −20 °C, 0 °C, rt, 50 °C.

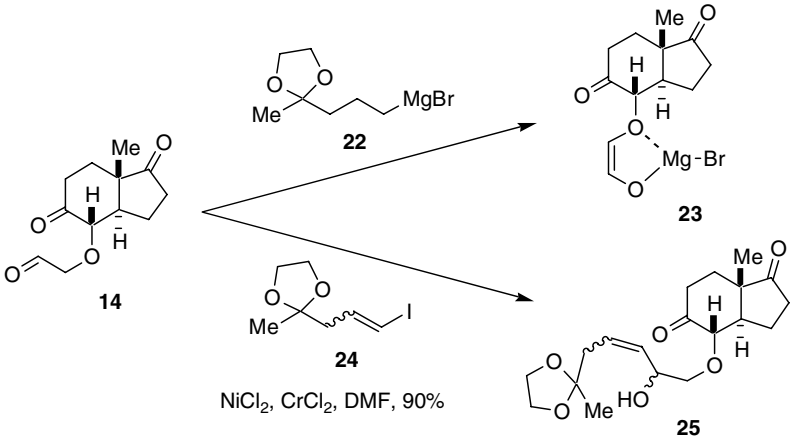
11c–g were applied to the O-alkylation with bromide **7** under various conditions. It turned out that most of the reactions resulted in complex mixtures including ethers **8**, elimination product **9** and bis-alkylated products **10** that were presumably produced through the epoxide intermediates.

After an extensive study along this line, the C–O bond formation was eventually achieved via O-alkylation of allyl alcohol **11e** with bromide **7** (Scheme 2), under the Ag_2O-molecular sieves condition.[10] The Ag_2O-mediated O-alkylation afforded the β-O-alkylated product **12** ($J^3_{\alpha\text{-H}} = 2.8$ Hz). It was then readily converted to the desired α-O-alkylated product **13** ($J^3_{\beta\text{-H}} = 12.8$ Hz) with K_2CO_3 in methanol, through the equilibration of the O-allyl group from the axial position to the equatorial position, which avoids the 1,3-diaxial interactions with the angular methyl group.

Oxidative cleavage of olefin **13** under the OsO_4–$NaIO_4$-2,6-lutidine condition[11] produced diketo-aldehyde **14**. It was anticipated that a nucleophilic chemoselective addi-



Scheme 2.



Scheme 3.

tion of a side chain to diketo-aldehyde **14** would lead to the secondary alcohol **16**, the precursor of compound **17** for intramolecular aldol condensations. Unexpectedly, this C–C bond formation turned out to be another difficult step. It was found that the addition of Grignard reagent **22** (Scheme 3) to diketo-aldehyde **14** under well-controlled conditions at low temperatures did not deliver compound **16**, but led to the recovery of the starting material **14** upon aqueous workup, while a complex mixture was produced under harsh conditions at high temperatures.

The unexpected behavior of diketo-aldehyde **14** might be associated with the unique electronic effects of the molecule. Presumably due to the field effects[12] of the two electron-withdrawing carbonyl groups as well as the electronegative inductive effect of the oxygen atom, in the presence of the basic Grignard reagent **22**, the electron-deficient carbonyl group might enolize and form the magnesium chelation complex **23**, which could be hydrolyzed back to compound **14** upon aqueous workup. Apparently, to overcome this problem, a non-basic chemoselective methodology was desired for this key C–C bond formation. To our delight, the Ni/Cr-mediated coupling[13] between diketo-aldehyde **14** and vinyl iodide **24** at room temperature successfully led to the C–C bond formation furnishing allylic alcohols **25**. More efficiently, by using chloride **15** and KI, a one-pot reaction of halogen exchange and Co/Cr-mediated coupling[14] directly generated the secondary alcohol **16** as a 1:1 mixture of two diastereomers. Dess–Martin oxidation[15] gave compound **17** and the subsequent cyclization, deprotection, and cyclization afforded compound **2**. Since the synthesis started with the commercially available optically pure (*S*)-Hajos–Parrish ketone, and the stereoselective reductive bromination produced *trans*-indane **7** whose configuration was not changed during the synthesis, our first enantioselective synthesis provided enantiopure compound **2** with the unambiguous *trans*-C/D ring junction.

The ^{1}H NMR spectral data of *trans*-oxa-steroid **2** were compared to those[4] of *cis*-oxa-steroid **3**. While the rest of their ^{1}H NMR spectra looked somewhat similar, the major difference between the *trans*- and *cis*-fused tetracyclic compounds is the chemical shift of the most characteristic proton H_8 (Fig. 3). For *cis*-oxa-steroid **3,** proton H_8 emerges at 3.78 ppm (d, $J_{8,14} = 9.6$ Hz), while for *trans*-oxa-steroid **2**, proton H_8 appears in a lower magnetic field at 4.23 ppm (d, $J_{8,14} = 9.6$ Hz), which implies that the chemical shift of the most characteristic proton H_8 could be used to differentiate the *trans*-fused ring junction from the *cis*-fused ring junction of this type of compounds. It is worthy to note that both *trans*-oxa-steroid **2** and *cis*-oxa-steroid **3** have the same coupling constant ($J_{8,14} = 9.6$ Hz) between protons H_8 and H_{14} in the *trans*-configuration, which indicates that a large coupling constant does not necessarily suggest a *trans*-fused ring junction.[4]

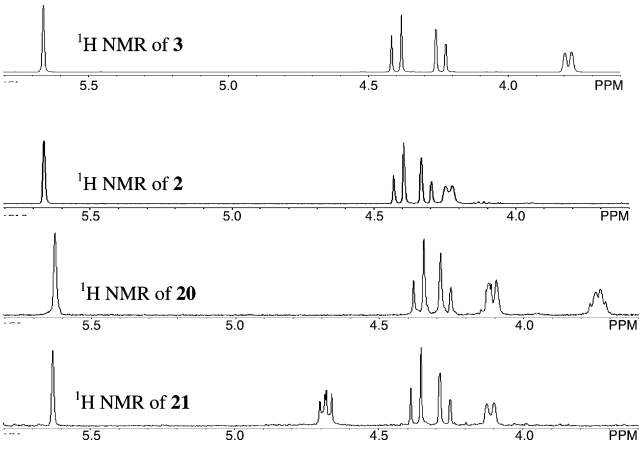


Figure 3.

Stereoselective reduction of the C-17 carbonyl group of compound **2** gave 17β-alcohol **20**. 17β-Acetate **21**[16] was prepared via acetylation of compound **20** in order to compare with the same compound[17] reported 30 years ago. While the rest of chemical shifts seem agreeable, the chemical shift of the most characteristic proton H_8 (4.11 ppm, d, $J_{8,14} = 9.6$ Hz for compound **21** in this study) was unfortunately omitted in the previous report[3] (Fig. 3). Consequently, the identity comparison of these two compounds seemed impossible, since the chemical shift of the most characteristic proton H_8, as discussed above, should be the key in differentiating the *trans*-fused ring junction from the *cis*-fused ring junction.

In addition to the discrepancy of their NMR data, another significant difference was the biological profile of the compounds that were derived from compound **2**. In contrast to the previous observation[3] that compounds derived from compound **2** were biologically inactive toward steroid receptors, we found that compounds derived from compound **2** not only retained excellent in vitro and in vivo biological activities of this type of natural steroids, but also exhibited outstanding better selectivity toward similar steroid receptors than the natural steroids.[18] Details of these studies will be reported in due course.

In conclusion, the first enantioselective synthesis of (8*S*,13*S*,14*R*)-7-oxa-estra-4,9-diene-3,17-dione with the unambiguous *trans*-fused ring junction was achieved in eight steps in 16.7% overall yield, which provides a useful template for developing novel biologically interesting oxa-steroids. Key features of the route included Ag_2O-mediated O-alkylation, thermodynamically controlled axial–equatorial inversion, one-pot of halogen exchange and Co/Cr-mediated coupling, and intramolecular aldol condensations.

Acknowledgments

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Supplementary data

Experimental and NMR spectra for selected compounds. Supplementary data associated with this article

can be found, in the online version, at doi:10.1016/j.tetlet.2006.11.042.

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16. *^{1}H NMR of compound* **21** *in this study*: ($CDCl_3$, 400 MHz) 0.96 (s, CH_3), 2.06 (s, CH_3), 4.11 (d, $J = 9.6$ Hz, CH), 4.27 (d, $J = 14.2$ Hz, CH), 4.37 (d, $J = 14.2$ Hz, CH), 4.68 (m, CH), 5.63 (s, CH).
17. *^{1}H NMR of compound* **21** *in Ref. 3*: ($CDCl_3$, 60 MHz) 0.95 (s, CH_3), 2.05 (s, CH_3), 4.31 (m, CH_2), 4.70 (m, CH), 5.62 (s, CH).
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