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Studies on the construction of abutasterone-type and 24-*epi*-abutasterone-type side chains employing asymmetric dihydroxylation of (*E*)-20(22),24-cholestadiene

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Abstract—The synthesis of abutasterone-type side chain, (20*R*,22*R*,24*S*)-20,22,24,25-tetrahydroxy-6β-methoxy-3α,5-*cyclo*-5α-cholestane **4**, and 24-*epi*-abutasterone-type side chain, (20*R*,22*R*,24*R*)-20,22,24,25-tetrahydroxy-6β-methoxy-3α,5-*cyclo*-5α-cholestane **6**, by means of Sharpless asymmetric dihydroxylation of (*E*)-20(22),24-cholestadiene **1** is described. Construction of abutasterone-type side chain **4** was carried out by selective mono-dihydroxylation of diene **1** with $(DHQ)_2AQN$, followed by dihydroxylation of the corresponding (24*S*)-hydroxy-20(22)-cholestene **2** with $(DHQD)_2AQN$. In contrast, bis-dihydroxylation of **1** with either $(DHQD)_2PHAL$ or $(DHQD)_2AQN$ preferentially occurs to produce 24-*epi*-abutasterone-type side chain **6**.

1. Introduction

Ecdysteroids are steroid hormones that regulate aspects of development, metamorphosis, reproduction, and diapause in all life cycle stages from newly laid eggs to adult insects.[1] Ecdysteroids are the steroid hormones of all classes of arthropods and possibly of other invertebrates. Ecdysteroids are found not only in insects, crustaceans, and other animal sources but also in many plant species. More than 300 different types of ecdysteroids have so far been isolated from animal and plant sources.

Although ecdysteroids are structurally quite different from mammalian steroids, the pharmacological effects of ecdysteroids on mammalians, including humans, have been widely reported,[2] such as growth-promoting effects, effects on cellular proliferation and differentiation, stimulatory effects of protein synthesis, improvements of both glucose and lipid metabolism, and neuromodulatory actions. Especially, ecdysteroids are widely used as inducers for gene-switch systems, which could be used in human gene therapy. Studies on these pharmacological effects have been considerably supported by the availability of ecdysteroids including their congeners. Since rare ecdysteroids have often been found as minor constituents, the development of a general method for the synthesis of ecdysteroids has become an important factor for quantitative bioassay.[3]

Abutasterone was isolated from the Amazonian plant, *Abuta velutina*,[4] and its epimer, 24-*epi*-abutasterone, was also isolated from *Vitex canescens*.[5] Furthermore, isolation of 24-hydroxylated ecdysteroids,[6] such as nusilsterone[6c] and pterosterone,[6d] have been reported. The commonly hydroxylated sites on the side chains are 20*R*, 22*R*, and 25, making 24-hydroxylated ecdysteroids quite rare. As part of our continuing studies on the synthesis of physiologically active steroids with highly oxygenated side chains,[7] we focused our attention on the synthesis of the abutasterone-type and its 24-epimer-type side chains. Herein, we report the construction of abutasterone-type and 24-*epi*-abutasterone-type side chains by means of Sharpless asymmetric dihydroxylation.[8] The strategy for the synthesis of both (20*R*,22*R*,24*S*)-tetraol **4**, an abutasterone-type side chain, and (20*R*,22*R*,24*R*)-tetraol **6**, a 24-*epi*-abutasterone-type side chain, was envisaged to employ (*E*)-20(22),24-cholestadiene **1**, readily prepared by Wittig olefination of the 20-keto steroid. Mono-dihydroxylation of diene **1** followed by successive dihydroxylation

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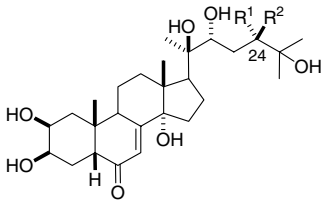
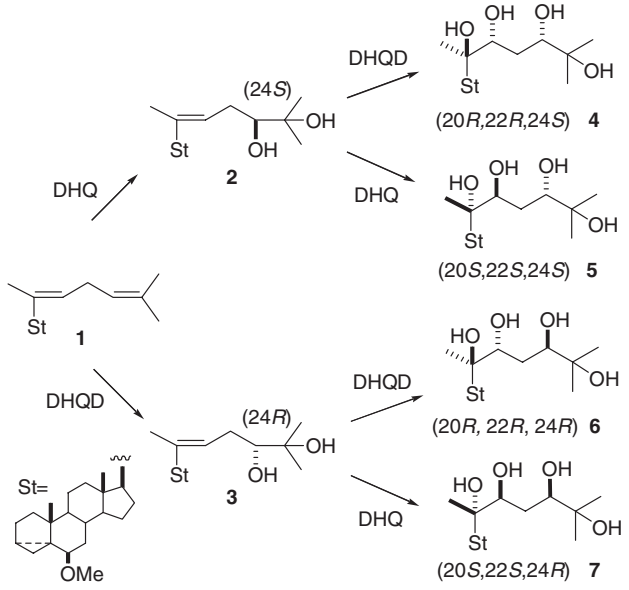


abutasterone R^1=OH, R^2=H
24-*epi*-abutasterone R^1=H, R^2=OH

of 20(22)-alkenes **2** and **3** with suitable chiral ligand combinations would occur regio- and diastereoselectively to provide **4** and **6** (Scheme 1).[9]

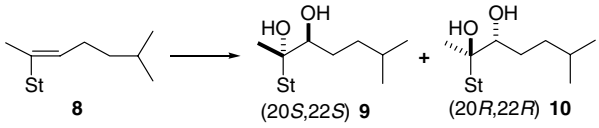


Scheme 1. Synthetic plan for the construction of abutasterone-type and 24-*epi*-abutasterone-type side chains.

2. Results and discussion

Ikekawa[10] and Gut[11] independently reported the dihydroxylation of (*E*)-20(22)-steroidal olefins with osmium tetroxide (OsO_4) leading to (20*S*,22*S*)-diols (unnatural form) preferentially. However extensive studies on the asymmetric dihydroxylation of (*E*)-20(22)-steroidal olefins have not yet been carried out. Thus, we first investigated the asymmetric dihydroxylation of (*E*)-20(22)-cholestene **8**,[11] as shown in Table 1. Since the reaction rate with a catalytic amount of OsO_4 and cooxidant was very sluggish, we used a stoichiometric amount of OsO_4 for the dihydroxylation. As expected, the dihydroxylation of **8** with dihydroquinine (DHQ) derived ligands would be matched reactions to afford exclusively **9** (entries 2, 4, and 8). In contrast, dihydroquinidine (DHQD) derived ligands, $(DHQD)_2PHAL$, DHQD-CLB, and $(DHQD)_2AQN$, gave moderate results due to mismatched reactions (entries 3, 5, and 9). Regarding the preparation of (20*R*,22*R*)-diol **10**[10b] (natural form), $(DHQD)_2AQN$ was the ligand of choice for the mismatched reaction.

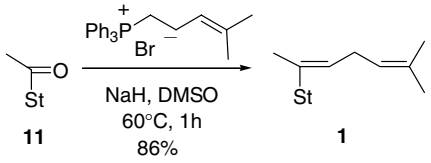
Table 1. Asymmetric dihydroxylation of (*E*)-20(22)-cholestene **8**[a]



Entry	Ligand	Yield (%)	Ratio of products[b]	
			9	**10**
1	None	66	96	4
2	$(DHQ)_2PHAL$	81	100	0
3	$(DHQD)_2PHAL$	90	64	36
4	DHQ-CLB	79	100	0
5	DHQD-CLB	74	59	41
6	$(DHQ)_2PYR$	84	97	3
7	$(DHQD)_2PYR$	84	87	13
8	$(DHQ)_2AQN$	92	100	0
9	$(DHQD)_2AQN$	83	57	43

[a] All reactions were run with a stoichiometric amount of osmium tetroxide.
[b] Determined by 270 MHz ^{1}H NMR spectral analysis.

(*E*)-20(22),24-Cholestadiene **1**, a key starting material, was prepared by Wittig olefination of 20-keto steroid **11**[10b] with 4-methyl-3-pentenylidenetriphenylphosphorane[12] in 86% yield (Eq. 1). The Wittig olefination of sterically hindered 20-keto steroids with unstabilized ylides occurs stereoselectively to give the *E*-isomers with no detectable *Z*-isomers.[13] The stereochemistry of the olefin was deduced by the chemical shifts of the 18- and 21-methyl protons, which appear at 0.58 and 1.64 ppm, respectively. The signals for the 18- and 21-methyl protons in the *E*-isomers occur at higher fields than would be expected for the *Z*-isomers (18-methyl protons: 0.65–0.78 ppm; 21-methyl protons: 1.68–1.71 ppm).[13,14]



(1)

Selective mono-dihydroxylation of (*E*)-20(22),24-cholestadiene **1** was examined as shown in Table 2. It is well known that the regioselectivity of the mono-dihydroxylation of a polyene is determined by electronic and steric effects.[8c] We supposed that steric effects might play a decisive role in controlling site-selectivity with respect to electronically similar double bonds and thus the less hindered 24-olefin could be osmylated preferentially. In the absence of a chiral ligand treatment of **1** with a stoichiometric amount of OsO_4 disappointingly gave almost equal amounts of mixture (24*R*)-diol **3** and tetraol **5** (entry 1). The use of DHQ derived ligands led to the formation of bis-dihydroxylated tetraols as minor products (entries 2, 4, 6, and 8). Pleasingly, $(DHQD)_2$-PHAL and $(DHQD)_2AQN$ gave complete regio- and diastereo-selectivities to produce only (24*R*)-hydroxylated product **3** (entries 3 and 9). A good level of regio- and diastereo-selection was observed as (24*S*)-diol **2** was found to be the major product in a ratio of (**2**/**3**/**5** =)82:2:16 with $(DHQ)_2AQN$ as the ligand (entry 8).