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Journal of Molecular Catalysis A: Chemical 253 (2006) 119–122
JOURNAL OF MOLECULAR CATALYSIS A: CHEMICAL
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Short communication

Synthesis of 7-dehydrocholesterol through a palladium catalyzed selective homoannular conjugated diene formation

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Received 27 January 2006; received in revised form 3 March 2006; accepted 6 March 2006
Available online 18 April 2006

Abstract

The development of a selective palladium catalyzed homoannular conjugated diene formation and its subsequent application to the synthesis of 7-dehydrocholesterol is reported.

Keywords: Palladium; Catalysis; Dehydrocholesterol; Elimination; Homoannular conjugated dienes

1. Introduction

Polyoxygenated sterols derivatives have been the subject of numerous studies in the last 10 years due to their potential biological activities. Such sterol metabolites have many important properties mostly related to the physiological control of cholesterol biosynthesis [1,2]. In this area, several investigators have demonstrated for example that oxygenated cholesterol such as 7-ketocholesterol and 25-hydroxycholesterol inhibit the activity of β-hydroxy-β-methylglutaryl CoA (HMG CoA) reductase, the rate-limiting enzyme in the biosynthesis of cholesterol, in various in vitro test system [3–7]. Recently, two new polyoxygenated sterols incrustasterol A and B possessing important cytotoxic activities against tumorous cells have been isolated from the marine sponge *Dysisdea incrustans* [8]. To date, all the synthesis of these products imply the use of 7-dehydrocholesterol **1** as starting material (Scheme 1).

Nevertheless, few methods exist for the synthesis of this latter derivative in quite good yield: the best result (57% yield) having been encountered by thermal decomposition of 7-benzyloxy cholesterol in refluxing dimethylaniline under CO_2 atmosphere [9]. The presence of homo- and heteroannular conjugated dienes in polycyclic systems are important in organic synthesis such as for 1α-hydroxyprovitamin D3 [10,11] or compactin. A variety of synthetic routes such as β-elimination of a 7-bromide [12] and a 7-tosylhydrazone [13] have been reported for a steroid 5-ene to a 5,7-diene. However, these processes involved the difficulty for separations of the desired 5,7-diene from the by-product 4,6-diene. In 1990, Tsuji et al. reported a highly selective method for homoannular conjugated dienes synthesis by the palladium catalyzed elimination of allylic esters [14]. In continuation of our work on biologically active sterol derivatives [15–17] and organopalladium chemistry we report herein the scope and limitation of such a method particularly suitable for the selective formation of 7-dehydrocholesterol.

At first, α-allylic compounds **5a**–**5c** (R′ = MeCO, CO_2Me, $COCF_3$) were prepared from cholesteryl acetate involving a stereoselective copper allylic benzoyloxylation key step [18] and the subsequent formation of diol precursor **4** in 61% yield. Synthesis of the corresponding allylic esters **5a**–**5c** was performed in pyridine in moderate to good yields varying from 55% to 91% (Scheme 2).

These different α-allylic steroidal derivatives **5a**–**5c** were involved in a subsequent palladium catalyzed elimination for the synthesis of homoannular conjugated dienes **7a**–**7c** in the B ring under various experimental conditions (solvent, temperature and palladium source). Thus, β-allylic esters **5a**–**5c** were treated with $Pd_2(dba)_3$/P(*n*-Bu)$_3$ or $Pd(OAc)_2$/P(*n*-Bu)$_3$ under various experimental conditions as outlined in Table 1 [19].

Whatever the experimental conditions the starting materials were recovered performing the reaction with substrates **5a** and **5b**. On the other hand, palladium catalyzed reaction of the

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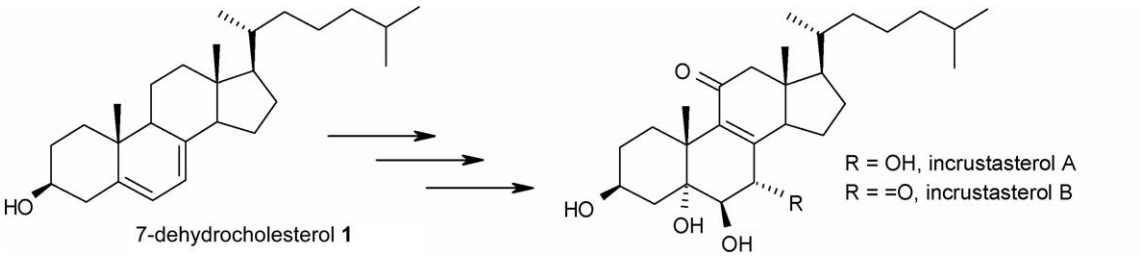
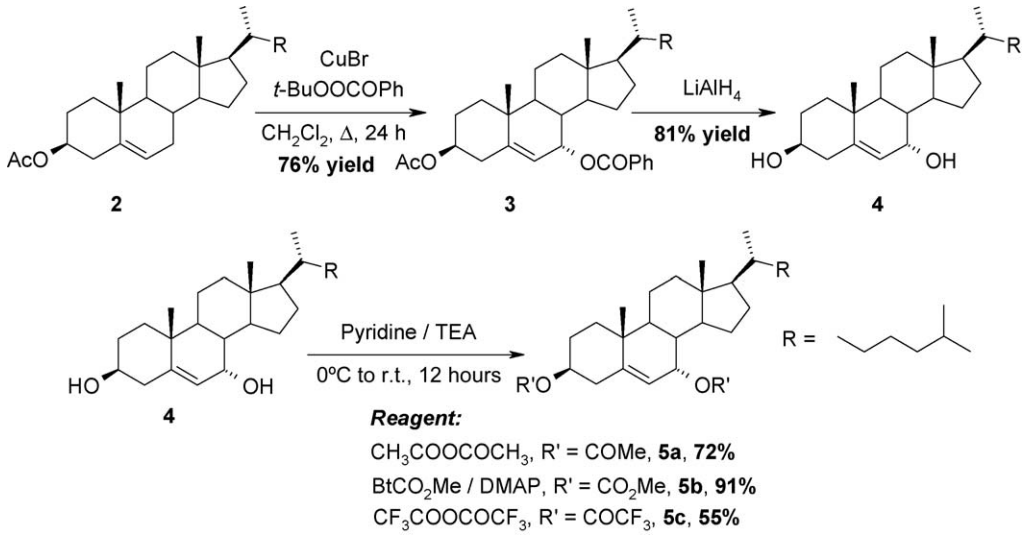
doi:10.1016/j.molcata.2006.03.014

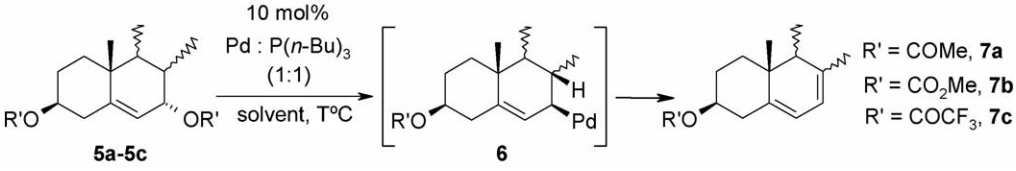


Scheme 1. Polyoxygenated sterols incrustasterol A and B issued from 7-dehydrocholesterol **1**.



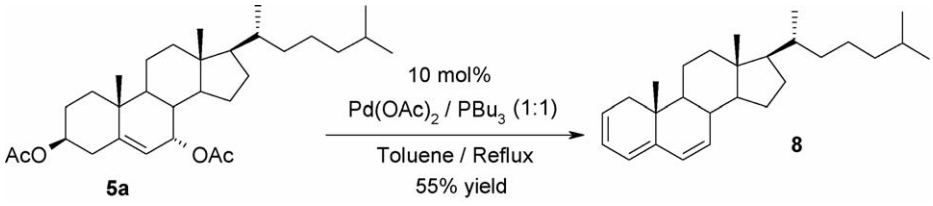
Scheme 2. Stereoselective synthesis of steroidal allylic esters **5a** and **5b**.

Table 1
Synthesis of homoannular conjugated dienes **7a**–**7c** under various experimental conditions

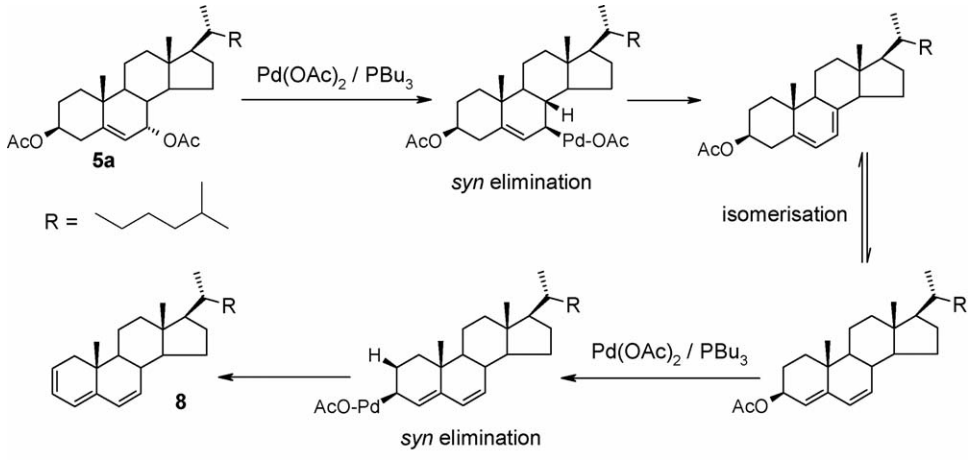


Entry[a]	Substrate	Solvent	Pd source	Yield of **7** (%)[b]
1	**5a**	THF	$Pd(OAc)_2$	<5
2	**5a**	CH_2Cl_2	$Pd(OAc)_2$	<5
3	**5a**	Toluene	$Pd(OAc)_2$	<5 (55)[c]
4	**5a**	Toluene	$Pd_2(dba)_3$	<5 (15)[c]
5	**5a**	Dioxane	$Pd(OAc)_2$	<5
6	**5b**	THF	$Pd(OAc)_2$	<5
7	**5b**	CH_2Cl_2	$Pd(OAc)_2$	<5
8	**5b**	Toluene	$Pd(OAc)_2$	<5
9	**5b**	Toluene	$Pd_2(dba)_3$	<5
10	**5b**	Dioxane	$Pd(OAc)_2$	<5
11	**5c**	Toluene	$Pd(OAc)_2$	12
12	**5c**	Dioxane	$Pd(OAc)_2$	23
13	**5c**	Dioxane	$Pd_2(dba)_3$	75

[a] Reactions performed on 13.5 mmol scale in refluxing solvent during 6 h under argon atmosphere.
[b] Isolated yield.
[c] Isolated yield mentioned in parenthesis corresponds to by-product.



Scheme 3. Synthesis of heteroannular triene **8**.



Scheme 4. Mechanistic rationale for the formation of heteroannular triene **8**.

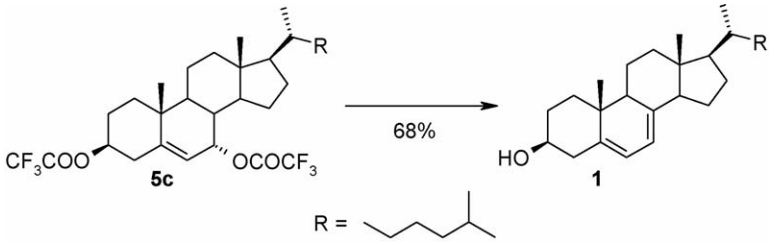
more reactive α-allylic trifluoroacetate **5c** gave the homoannular conjugated diene **7c** in 75% yield performing the reaction in refluxing dioxane using $Pd_2(dba)_3$/P(*n*-Bu)$_3$ catalyst system (Table 1, entry 13). Low chemical yield of up to 23% has been observed using $Pd(OAc)_2$/PBu_3 catalyst (Table 1, entry 12). In these two cases, treatment of the 7α-trifluoroacetate **5c** afforded the 5,7-diene **7c** regioselectively and no heteroannular diene was detected. Thus, in the intermediate complex **6**, the β-oriented 7σ-allylpalladium undergoes facile *syn*-elimination of 8β-hydrogen to afford **7c** exclusively.

As already mentioned, no formation of homoannular conjugated diene **7a** has been noticed from derivative 5α performing the reaction in refluxing toluene in the presence of 10 mol% of $Pd(OAc)_2$/P(*n*-Bu)$_3$ catalyst. Formation of an unexpected heteroannular triene **8** has been detected and the product has been isolated in 55% yield and fully characterized by NMR and mass spectroscopy (Scheme 3) [20]. Nevertheless, this reaction appears highly solvent and temperature dependent since no formation of such by-product was observed performing the reaction in refluxing THF, CH_2Cl_2 or dioxane.

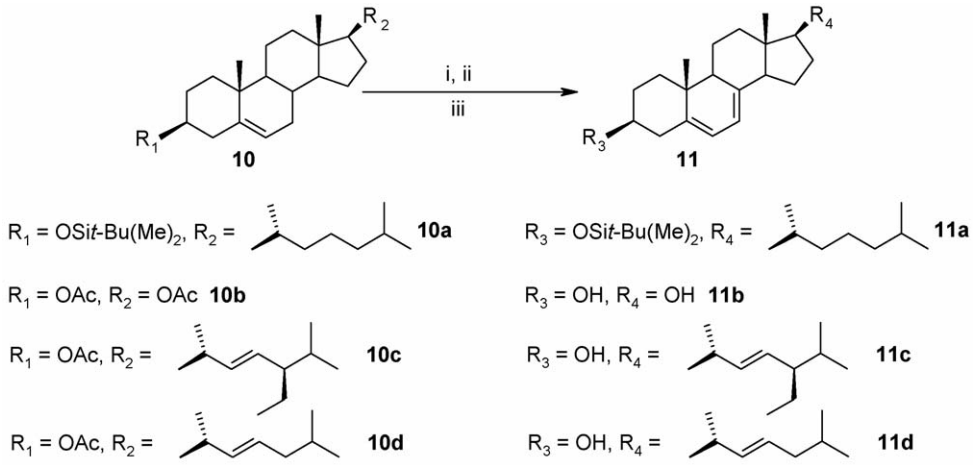
The formation of product **8** can be rationalized through a *syn*-elimination-isomerisation-*syn*-elimination process occurring exclusively in refluxing toluene since the isomerisation process occurs only at temperature higher than 80 °C (Scheme 4).

Finally, the synthesis of 7-dehydrocholesterol **1** was realized in a three steps synthesis from cholesterylacetate **9** in 42% overall yield involving the formation of a homoannular conjugated diene as key intermediate (Scheme 5) [21].

In order to clarify the scope of the present reaction, we examined selective palladium catalyzed homoannular conjugated diene formation of a series of cholesterol derivatives by using the best experimental conditions previously encountered. Results are summarized in Scheme 6.



Scheme 5. Synthesis of 7-dehydrocholesterol **1**. Conditions: (a) $Pd_2(dba)_3$:P(*n*-Bu)$_3$(1:1) dioxane, reflux, 8 h. (b) $LiAlH_4$, THF, −20 °C.



Scheme 6. Palladium catalyzed homoannular conjugated diene formation of various cholesterol derivatives **11a**–**11d**. Conditions: (i) see Ref. [18], (ii) (a) $LiAlH_4$, THF, −20 °C; (b) pyridine, $CF_3COOCOCF_3$, 0 °C to r.t. 12 h, (iii) (a) $Pd_2(dba)_3$:P(*n*-Bu)$_3$ (1:1), dioxane, reflux, 8 h; (b) $LiAlH_4$, THF, −20 °C. Overall yield **11a** (32%), **11b** (21%), **11c** (42%), and **11d** (52%).

Whatever the considered sterol derivative nature, the reaction proceeds in moderate chemical overall yields varying from 21% to 52% but always with a total selectivity [22–25].

In conclusion, the development of a selective palladium catalyzed homoannular conjugated diene formation highly substrate dependent and its subsequent application to the synthesis of 7-dehydrocholesterol and other sterol derivatives has been reported.

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[18] J.M. Brunel, L. Billottet, Y. Letourneux, Tetrahedron: Asymmetry 16 (2005) 3036.
[19] General procedure for the synthesis of homoannular conjugated diene **7c**: to a stirred solution of $Pd(dba)_2$ (7.7 mg; 1.35×10^{-5} mol) in dioxane (3 mL) was added a solution of the P(*n*-Bu)$_3$ (3 μl, 1.35×10^{-5} mol) in dioxane (2 mL) under an argon atmosphere. After stirring for 15 min at reflux, a solution of difluoroacetate cholesteryl derivative **5c** (80 mg; 13.5 mmol) in dioxane (2 mL) was added. After stirring for 5 min, NEt_3 (56 μL, 40.4 mmol) were added *via* syringe. The reaction mixture was stirred for 6 h and monitored by TLC analysis. After completion of the reaction, the mixture was concentrated in vacuo. The oily residue was purified by chromatography on a silicagel column using EtOAc/petroleum ether as eluent (2/8) affording the expected homoannular conjugated diene **7c** in 75% yield. Viscous oil; ^{1}H NMR: δ = 0.65–2.58 (m, 40H), 3.47–3.54 (m, 1H), 4.88–5.97 (m, 2H); ^{13}C: δ = 12.31, 15.02, 18.99, 19.60, 23.44, 23.61, 24.34, 24.90, 27.03, 28.90, 30.29, 30.96, 32.85, 33.12, 36.71, 37.04, 38.31, 40.36, 43.24, 43.70, 49.78, 56.77, 57.00, 74.59, 120.23, 125.95, 136.12, 149.57, 157.44.
[20] Triene **8**: viscous oil; ^{1}H NMR: δ = 0.28–2.03 (m, 37H), 5.31–6.29 (m, 5H); ^{13}C: δ = 11.77, 15.25, 18.60, 20.84, 22.50, 22.76, 23.84, 27.89, 28.13, 35.45, 35.72, 36.10, 36.31, 39.42, 42.98, 51.42, 54.45, 56.02, 119.16, 124.13, 125.01, 127.92, 131.35, 142.58. It is noteworthy that we have not tried to isolate this derivative performing the reaction in refluxing toluene and starting from allylic carbonate **5b** but it must be present since all the experimental conditions are required.
[21] 7-Dehydrocholesterol **1**: white solid; ^{1}H NMR: δ = 0.60–2.43 (m, 40H), 3.46 (s, 1H), 3.61 (m, 1H), 5.36–5.38 (m, 1H), 5.54–5.56 (m, 1H); ^{13}C: δ = 12.21, 16.68, 19.24, 21.51, 22.95, 23.21, 23.87, 24.27, 28.40, 32.35, 36.54, 37.40, 38.77, 39.56, 39.90, 41.15, 43.31, 46.63, 51.16, 54.89, 56.28, 70.83, 116.66, 120.00, 140.15, 141.82.
[22] Sterol derivative **11a**: viscous clear oil; ^{1}H NMR: δ = 0.06 (s, 6H), 0.60 (s, 3H), 0.82–3.52 (m, 47H), 5.35–5.42 (m, 2H); ^{13}C: δ = −4.57, 11.95, 16.32, 18.20, 19.52, 21.10, 22.90, 23.15, 24.15, 25.85, 28.10, 31.12, 33.95, 36.45, 37.32, 40.21, 43.28, 46.31, 54.65, 56.32, 72.62, 109.71, 129.01, 139.20, 139.55.
[23] Sterol derivative **11b**: viscous clear oil; ^{1}H NMR: δ = 0.69 (s, 3H), 0.91–3.76 (m, 21H), 5.34–5.52 (m, 4H); ^{13}C: δ = 16.01, 20.12, 26.01, 31.29, 32.58, 35.56, 37.42, 38.60, 41.06, 41.82, 44.90, 49.42, 69.71, 81.48, 119.21, 121.23, 140.14, 141.95.
[24] Sterol derivative **11c**: viscous clear oil; ^{1}H NMR: δ = 0.64 (s, 3H), 0.71–4.34 (m, 49H), 5.00 (m, 1H), 5.41 (m, 2H), 5.43 (m, 1H), 5.57–5.60 (m, 1H); ^{13}C: δ = 12.06, 16.20, 18.75, 19.21, 20.32, 21.02, 23.14, 26.54, 32.22, 34.58, 37.24, 37.98, 39.54, 41.35, 43.01, 44.77, 46.88, 54.55, 55.76, 69.71, 117.65, 119.38, 131.17, 135.23, 140.70.
[25] Sterol derivative **11d**: viscous clear oil; ^{1}H NMR: δ = 0.65 (s, 3H), 0.81–2.50 (m, 34H), 3.65 (m, 1H), 5.14–5.29 (m, 2H), 5.40–5.42 (m, 1H), 5.57–5.60 (m, 1H); ^{13}C: δ = 12.43, 16.67, 18.30, 20.04, 20.35, 21.49, 23.39, 28.68, 31.30, 32.38, 33.48, 37.42, 38.85, 39.48, 40.82, 41.18, 43.22, 46.65, 54.95, 56.12, 70.82, 116.69, 119.98, 132.37, 135.96, 140.19, 141.72.