Synthesis of (3S)-Hydroxyandrosta-5,7-diene-17-ones via Intramolecular Cobalt-Mediated [2+2+2] Cycloaddition¹

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Abstract: A new method for the synthesis of lumisterin-type steroids following the D \rightarrow ABCD approach is reported. A key step is the cobalt-induced cyclization of a cyclopentanoid enediyne, which was prepared via thioalkylation of the zinc enolate of a 2,3-substituted cyclopentanone with α -chlorosulfides.

Key words: cobalt, cycloaddition, cyclopentanones, steroids, vitamins

Recently, we reported the cobalt-mediated [2+2+2] cycloaddition of 4-hydroxy-substituted enediynes² towards 2-hydroxy-substituted decahydrophenanthrenes.³ The hydroxy group in the propargylic position was tolerated under the chosen reaction conditions. Furthermore, it has been demonstrated that this stereogenic center does not have any influence on the formation of the stereogenic centers from the Z double bond, which were transformed to trans-phenanthrenes in a diastereomeric ratio of almost 1:1. These *trans*-phenanthrenes represent the ABCframework of ergosterin or lumisterin. Consequently, a diastereoselective synthesis of (3S)-hydroxyandrosta-5,7diene-17-ones 1, precursors of vitamin D, was envisioned by following the D-ABCD approach. Recently, Malacria reported the preparation of 11-aryl-substituted steroids via cobalt(I)-mediated cyclization of allenediynes.⁴

In this convergent synthesis, the racemic ring D (building block 9) and the alkene side chain 7 were connected by a

thioalkylation reaction⁵ at a very late stage of the synthesis (Scheme 1). The PG²-protected hydroxy group of cyclopentanone **3** was then converted after deprotection, oxidation, and a Corey–Fuchs alkynation to the desired triple bond in **2**. After cleavage of the protective group PG¹ and Swern oxidation, we introduced the propargylic moiety enantiomerically using a chiral boron–allene complex.⁶ Cobalt-mediated cyclization of enediyne **2** should afford either ergosterin or lumisterin-type steroids. The simultaneous formation of the sterogenic center at C-9 and C-10 of the steroid should be exclusively induced by the *trans*-configured centers at C-2 and C-3 of the cyclopentanone precursor since the stereogenic center in the sidechain at C-7' does not have any stereochemical influence on the outcome of this cyclization.²

For the synthesis of the α -chlorosulfides **7** we started from the TBDMS-⁷, TBDPS-,⁸ and Bn⁹-O-protected pentynols **4** (Scheme 2). After Cp₂ZrCl₂-catalyzed carbo-alumination of **4** the corresponding vinyl alanes were treated with *n*-BuLi and ethylene oxide to afford the *E*-alkenols **5**.² The alcohols **5** were mesylated and then transformed into the phenylsulfides **6** by reaction with KSPh in dimethyl-sulfoxide at room temperature. Finally, chlorination with *N*-chlorosuccinimide in CCl₄ gave the chlorides **7**.

The synthesis of the cyclopentanones 9 was achieved starting from the known racemic 3-hydroxymethyl-2methylcyclopentanone 8 by protection of the hydroxy



Scheme 1

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Scheme 2 *Reagents and conditions*: (a) (i) AlMe₃ (3 equiv), Cp_2ZrCl_2 (40 mol%), toluene, 0 °C, 30 min, then 4, 50 °C, 76 h; (ii) *n*-BuLi (3 equiv), -65 °C to -40 °C, then ethylene oxide (3.5 equiv); (b) Et₃N (1.5 equiv), MsCl (1.1 equiv), CH_2Cl_2 , -10 °C, 15 min; (c) *t*-BuOK (1.2 equiv), PhSH (1.2 equiv), DMSO, r.t., 1 h; (d) NCS (1.3 equiv), CCl₄, r.t., 12 h. **7a**: R¹ = TBDMS (60% overall yield), **7b**: R¹ = TBDPS (55% overall yield), and **7c**: R¹ = Bn (44% overall yield).

group as its silyl ether *rac*-**9a** (TBDMSCl and imidazole), as its benzoate ether *rac*-**9b** (BzCl and pyridine), or as its benzyl ether *rac*-**9c** (benzyltrichloroacetimidate) (Scheme 3).¹⁰

The α -thioalkylation of cyclopentanones **9** was achieved by deprotonation of these cyclopentanones with potassium hydride, transmetalation of the generated enolates with ZnCl₂ into the zinc enolates and reaction with the α -chlorophenyl sulfides **7**. However, only alkylation of the TBDMS-O-protected cyclopentanone **9a** with the TBDPS- and Bn-O-protected alkenes **7b** and **7c** was successful. While reductive desulfurization of *rac*-**10c** with lithium in diethyl amide gave the desired alkene **11** with concomitant cleavage of the benzyl protecting group, the



Scheme 3 *Reagents and conditions*: (a) rac-9a: R² = TBDMS, TBDMS-Cl (1.2 equiv), imidazole (2.5 equiv), DMF, 0 °C to r.t., 3 h (70%); rac-9b: R² = Bz, BzCl (1.25 equiv), pyridine (1.25 equiv), CH₂Cl₂, r.t., 18 h (74%); rac-9c: R² = Bn, BnOC=NHCCl₃ (2 equiv), CH₂Cl₂-THF (5:1), 0 °C, 2 h (60%).

LETTER

silyl protected *rac*-10b decomposed under the same conditions. Protection of 11 with TBDPSCl and imidazole, resulted in cleavage of the TBDMS group under mild conditions and Swern oxidation of the alcohol obtained provided the aldehyde *rac*-12. Corey–Fuchs alkynation,¹¹ desilylation with TBAF·3H₂O, and oxidation under the same conditions as above gave aldehyde *rac*-13, which was converted to the enediyne 14 using Yamamoto's chiral allenylboronic ester⁶ and protection of the propargylic alcohol obtained as its MEM ether.

Subsequent CpCo(CO)₂-mediated [2+2+2] cycloaddition of the diastereomeric pair **14/14'** (1:1) in refluxing toluene with exposure to visible light followed by oxidative demetallation with FeCl₃ afforded the (3*S*)-hydroxyandrosta-5,7-diene-17-ones **15** (Scheme 5).¹² Both the ratio and the absolute configuration of the obtained steroids were determined by comparison of their ¹³C NMR spectra with the ¹³C NMR spectrum of an authentic sample of (3 β)-3methoxyethoxymethoxyandrosta-5,7-dien-17-one **17**.¹⁴



Scheme 4 *Reagents and conditions*: (a) KH (1 equiv), THF, r.t., then ZnCl_2 (2.5 equiv), $-15 \degree \text{C}$ to $-80 \degree \text{C}$, then **7**, $-80 \degree \text{C}$ to r.t., 15 h; **7b**: $R^1 = \text{TBDPS}$ (32%, **10b**); **7c**: $R^1 = \text{Bn}$ (35%, **10c**); (b) $R^1 = \text{Bn}$, Li (3 equiv), EtNH₂, $-20 \degree \text{C}$ to reflux (68%); (c) TBDPSCl (1.2 equiv), imidazole (2.5 equiv), DMF, r.t. (94%); (d) 1% HCl in EtOH, r.t., 2 h (80%); (e) (COCl)₂, Et₃N, DMSO, CH₂Cl₂, $-65 \degree \text{C}$ (94%); (f) (i) PPh₃ (4 equiv), CBr₄ (2 equiv), CH₂Cl₂, 0 °C, 30 min, then **12**, 30 min (76%); (ii) *t*-BuLi (3 equiv), THF, $-80 \degree \text{C}$, 30 min (78%); (g) TBAF·3H₂O (1.2 equiv), THF, r.t., 4 h (90%); (h) (COCl)₂, Et₃N, DMSO, CH₂Cl₂, $-65 \degree \text{C}$ (78%); (i) CH₂=C=CHB(OH)₂ (1 equiv), D-(-)-diisopropyl tartrate (2 equiv), toluene, $-80 \degree \text{C}$, then **13**, 24 h (78%); (j) *i*-Pr₂NEt (1.5 equiv), CH₃OCH₂CH₂OCH₂Cl (1.5 equiv), CH₂Cl₂, 0 °C to r.t., 18 h (88%).

This was synthesized starting from commercially available¹³ (3β)-3-androsta-5-en-17-one **16** by employing the phenylsulfoxide method of Confalone and co-workers (Scheme 6).¹⁴

Starting from a 1:1 mixture of 14 and 14' the formation of the stereogenic centers C-9 and C-10 should be controlled only by the cyclopentanoid moiety. Consequently, the diastereomeric pairs 15a/15'a and 15b/15'b must be obtained each in a 1:1 ratio. The lumisterin and ergosterin precursors ratio of 15a/15b was found to be 7:1 after the ¹³C NMR data of 15b were determined, which coincided with those of 17, prepared from 16 (Scheme 6). Table 1 shows selected data and the ratio of the prepared steroids.







In summary, the formation of the tetracyclic core 1 is reported via an intramolecular cobalt-mediated [2+2+2] cycloaddition of an enediyne, which has been synthesized starting from a substituted thiochloride and a 2,3-disubstituted cyclopentanone. Since several chiral syntheses of

| Table 1 Selected ¹³ C NMR d | data |
|--|------|
|--|------|

| Steroid ^a | 15a | 15′a | 15′b | 15b | 17 ^b | |
|----------------------|--------|--------|--------|--------|------------------------|--|
| C-3 | 70.74 | 75.81 | 71.00 | 75.31 | 75.32 | |
| C-5 | 140.82 | 142.15 | 139.16 | 141.16 | 141.14 | |
| C-6 | 120.00 | 119.66 | 119.54 | 119.21 | 119.22 | |
| C-18 | 13.66 | 13.81 | 13.95 | 13.51 | 13.50 | |
| Ratio | 7 | 7 | 1 | 1 | _ | |

^a Chemical shift in ppm.

^b Prepared from **16** in enantiomerically and diastereomerically pure form.

substituted cyclopentanones and cyclopentanes are wellknown,^{1a} the synthesis of the steroid skeleton described herein offers a new convergent approach to vitamin D compounds (deltanoids) following the construction principle D \rightarrow ABCD. Extension of this strategy to the synthesis of substituted steroids (provitamin analogues), which can been transformed directly, after photolysis and thermal isomerization, to related vitamin D is under investigation.

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- (12) **Cobalt-mediated [2+2+2] cycloaddition:** A solution of enediyne **14** (200 mg, 0.54 mmol) in toluene (80 mL) was cooled to -70 °C and the apparatus was evacuated for 3 min (0.5 Torr). The flask was allowed to warm to r.t. and the apparatus was filled with argon. The solution of enediyne in toluene was cooled to -70 °C and the above procedure was repeated twice. CpCo(CO)₂ (117 mg, 0.65 mmol) was added and the reaction mixture was refluxed under radiation with visible light until no starting material could be detected by TLC analysis. The reaction mixture was cooled to r.t. and volatile components were removed in vacuo (20 °C/0.1

Torr). The residue was dissolved in degassed Et_2O -pentane (1:4, 10 mL) and filtered through celite under an argon atmosphere. FeCl₃·H₂O (0.49 g, 1.8 mmol) was dissolved in MeCN (20 mL), pentane (20 mL) was added and the mixture cooled to -20 °C. At this temperature the filtrate was added under stirring, and stirring was continued for 30 min. The reaction mixture was cooled to -60 °C and the pentane layer was removed from the frozen MeCN layer. The MeCN layer was allowed to warm to -20 °C, pentane (15 mL) was added, and the above procedure was repeated four times. The pentane layers were combined, the solvent was removed in vacuo (30 °C/18 Torr), and the residue purified by chromatography on silica gel (Et₂O-pentane, 1:1) to afford steroids **15** (66.65 mg, 0.18 mmol, 33%).

Compound 15a/15'a (signals of the major diastereomeric pair): $R_f = 0.27$ (Et₂O–PE, 1:1). ¹H NMR (250 MHz, $CDCl_3$): $\delta = 0.76$ and 0.84 (2 s, 6 H, 2 × CH₃), 1.20–2.80 (m, 16 H, CH₂, CH), 3.40 (s, 3 H, OCH₃), 3.50-3.64 and 3.66- $3.79 (2 \times m, 5 H, OCH_2CH_2O, OCH), 4.78 (dd, J = 6 Hz)$ 6 Hz, 2 H, OCH₂O), 5.47–5.68 (m, 2 H, C=CHC=CH). ¹³C NMR (50.3 MHz, CDCl₃): δ = 13.66 and 13.81 (C-18), 18.05, 18.38, 20.20, 20.23, 26.17, 28.80, 29.06, 33.96, 35.78, 35.85, 35.93, 36.12, 37.08, 38.03, and 38.28 (C-1, C-2, C-4, C-10, C-11, C-12, C-15, C-16), 20.30 (C-19), 46.27 and 46.58 (C-9), 46.77 (C-13), 59.04 (C-23), 66.78 and 71.79 (C-21, C-22), 70.74 and 75.81 (C-3), 93.35 and 93.73 (C-20), 116.50, 116.57, 119.66 and 119.99 (C-6, C-7), 137.46, 137.94, 140.82 and 142.15 (C-5, C-8), 220.97 and 221.15 (C-17). MS (70 eV): m/z (%) = 374 (2) [M⁺], 268 (100) $[M - C_4 H_{10} O_3]^+$, 89 (35) $[C_4 H_{10} O_3^+]$, 59 (60) $[C_{3}H_{7}O^{+}]$. HRMS: *m*/*z* calcd $C_{23}H_{34}O_{4}$ for 374.2457; found: 374.2459.

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