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A Formal Synthesis of Betamethasone

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A formal synthesis of betamethasone from 5α-pregnane-3β,16β,20*S*-triol is described. Key transformations are a bromination-acetylation of triol, an S_N2 reaction of the resulting C16α-bromide with dimethylcopperlithium to get the required C16β-methyl group, and a double hydroxylation to prepare the dihydroxyacetone side chain.

Keywords betamethasone, pregnanetriol, formal synthesis, C16β-alkyl group, double epoxidation

Introduction

Betamethasone (**1**) is a potent glucocorticoid steroid with anti-inflammatory and immunosuppressive properties, and has been included in the WHO model list of essential medicines as an anti-inflammatory and anti-pruritic medicine.[1] Its esters such as 17-valerate and 17,21-dipropionate are also potent anti-inflammatory agents used in dermatological therapies.[2]

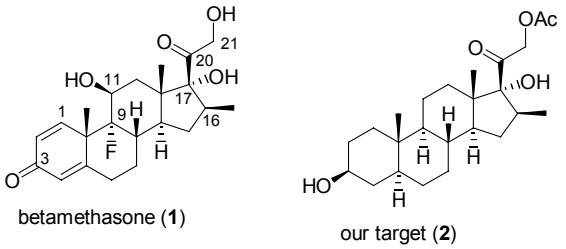

Figure 1 Structures of betamethasone (**1**) and our target (**2**).

How to introduce the C16-methyl group was the key challenge in betamethasone synthesis, hence, drew most attention from synthetic community.[3] With **5** and **6** as synthetic intermediates for the synthesis of **1**, several methods have been developed and Scheme 1 depicted three most practiced strategies. Depending on structural features of the starting materials (C17-ketone **3** or the enone **7**), the characteristic C16β-Me was introduced through a three-step alkylation (from **3** to **4**),[3e] through an epoxide-opening process (from **7** to **8** to **5**),[3f] or through a process where a [3+2]/retro-[3+2] cycloaddition with diazomethane (from **7** to **9**) was followed by a catalytic hydrogenation (from **9** to **10**).[3b-d] The side chain was then installed or modified accordingly. For example, compound **4** was converted to **5** via cyanohydrination of the C17 ketone and MeLi addition, whereas **10** via enol ether formation and oxidation of the C20 ketone. Methyl ketone **5** routinely underwent halogenation and substitution with KOAc to get the required C21-OH installed. Herein, from another perspective for introducing C16β-Me, we report a synthesis of compound **2**, an advanced intermediate for betamethasone,[4] from 5α-pregnane-3β,16β,20*S*-triol (**11**).

Our group have explored the reactivities and selective transformations of **11**, and used the results in the synthesis of natural products and drugs.[5] The hydroxyl groups of **11** at the C16 and the C20 offered a chance to synthesize betamethasone. Our previous attempt employing an epoxide-opening strategy was not effective.[6] Therefore, we decided to probe the possibilities of using C16-OH to introduce C16-Me through S_N2 reaction and using C20-ketone to introduce its neighboring hydroxyls through oxidation.

Experimental

16α-Bromo-3β-((*tert*-butyldimethylsilyl)oxy)-pregnane-20*S*-ol (15) from pregnanetriol (11)

To a suspension of pregnanetriol **11** (150 g, 445 mmol) in toluene (350 mL) was added a solution of HBr in HOAc (35%, 150 mL). The mixture was stirred for 60 min in an oil bath preheated to 45 ℃, then water (200 mL) and NaOAc (41.5 g) were added. The mixture was separated and the aqueous layer was extracted with toluene (200 mL). The combined organic layers were washed with brine and concentrated under reduced pressure to give a dark brown wax, which was dissolved in MeOH/THF (300 mL/100 mL) and treated with $LiOH•H_2O$ (30.0 g, 710 mmol) at reflux for 2 h, then concentrated under reduced pressure to remove the solvents. The residue was dissolved with dichloromethane (500 mL), washed with water and brine, dried over Na_2SO_4, and filtered to remove the drying agent. To the

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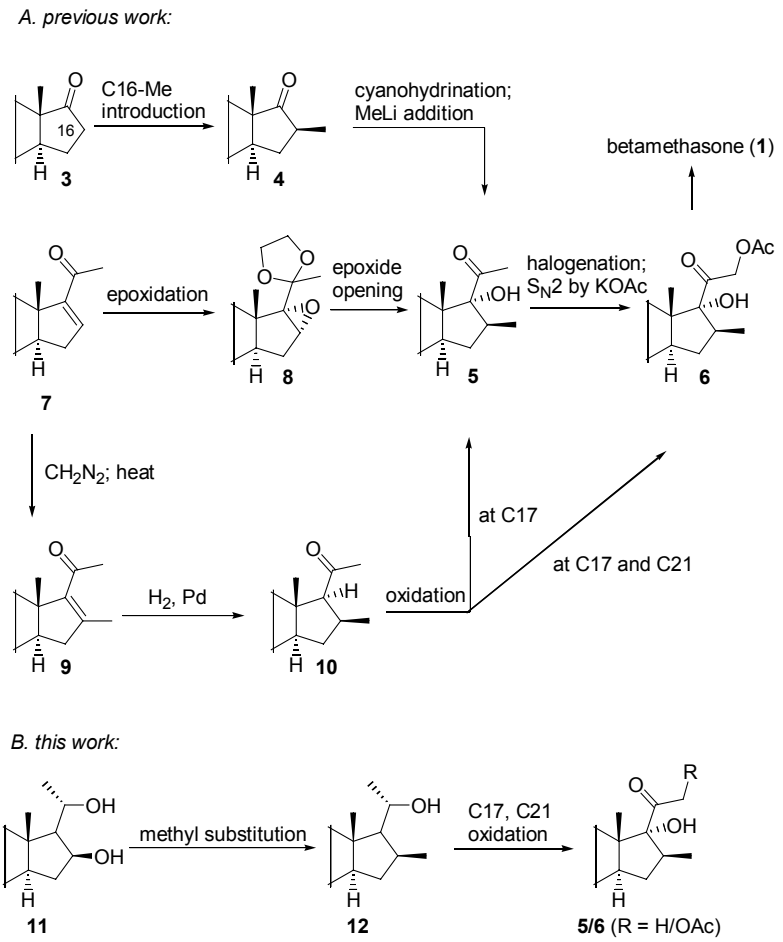
Scheme 1 Key steps in the syntheses of betamethasone (the ABC rings were omitted for clarity)



solution were added immidazole (75.8 g, 1.1 mol), DMAP (2.69 g, 22 mmol) and TBSCl (100 g, 667 mmol) at ambient temperature. The mixture was stirred for 3 h and quenched by adding water and separated. The aqueous layer was extracted with dichloromethane (250 mL); the combined organic layers were washed with brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude was recrystalized with hexane to provide **15** (138 g, 268 mmol, 60%) as white crystals. m.p. 160－161 ℃; $[\alpha]_D^{23}$ ＋7.0 (*c* 1.03, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) *δ*: 4.46 (t, *J*＝7.3 Hz, 1H), 3.80－3.88 (m, 1H), 3.50－3.57 (m, 1H), 1.29 (d, *J*＝6.3 Hz, 3H), 0.87 (s, 9H), 0.78 (s, 3H), 0.64 (s, 3H), 0.03 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) *δ*: 72.1, 69.5, 68.3, 54.3, 53.2, 51.2, 45.1, 44.3, 39.0, 39.0, 38.7, 37.2, 35.7, 34.3, 32.1, 32.0, 28.7, 26.1, 24.5, 20.8, 18.3, 13.5, 12.5, –4.4; IR (KBr film) *ν*: 3554, 3397, 2930, 2855, 1471,1461, 1448,1386, 1253, 1098, 835, 773 cm^{-1}; MS-ESI (*m/z*): 535.2 $[M＋Na]^+$. Anal. calcd for $C_{27}H_{49}BrO_2Si$: C 63.13, H 9.62; found C 63.31, H 9.72.

16*β*-Methyl-3*β*-((*tert*-butyldimethylsilyl)oxy)-pregnane-20*S*-ol (16)

Under argon atmosphere, to a suspension of bromide **15** (20.56 g, 40 mmol) and CuI (9.12 g, 48 mmol) in anhydrous THF (160 mL) at 0 ℃ was added MeLi (48 mL, 3.0 mol/L in diethoxymethane, 144 mmol) over 20 min. The ice bath was removed and the reaction mixture was allowed to stand at ambient temperature for 5 h and quenched with saturated NH_4Cl solution (200 mL). The mixture was stirred in the air for 15 h and diluted with ether/ethyl acetate (300 mL/200 mL) and separated. The aqueous layer was extracted with ether (200 mL). The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated to provide crude **16** (18.2 g, 40 mmol) which was used in the next step without purification. m.p. 192－193 ℃; $[\alpha]_D^{23}$ ＋16 (*c* 1.01, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) *δ*: 3.87－3.92 (m, 1H), 3.49－3.57 (m, 1H), 2.23－2.35 (m, 1H), 1.93－1.97 (m, 1H), 1.82－1.86 (m, 1H), 1.25 (d, *J*＝6.1 Hz, 3H), 1.14 (d, *J*＝7.2 Hz, 3H), 0.87 (s, 9H), 0.78 (s, 3H), 0.68 (s, 3H), 0.04 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) *δ*: 72.3, 67.3, 61.1, 55.8, 54.5, 45.1, 42.7, 40.0, 38.8, 37.3, 35.6, 35.5, 35.0, 32.6, 32.2, 32.1, 28.9, 26.1, 24.0, 21.0, 19.3, 18.4, 13.8, 12.5, –4.4; IR (KBr film) *ν*: 3510, 2931, 2857, 1472, 1461, 1435, 1380, 1252, 1100, 870, 774 cm^{-1}; MS-ESI (*m/z*): 471.4 $[M+Na]^+$. Anal. calcd for $C_{28}H_{52}O_2Si$: C 74.93, H 11.68; found C 74.90, H 11.66.

16*β*-Butyl-3*β*-((*tert*-butyldimethylsilyl)oxy)-pregnane-20*S*-ol (16a)

Under argon atmosphere, to a suspension of bromide

15 (1.03 g, 2.0 mmol) and CuBr•Me_2S (617 mg, 3.0 mmol) in anhydrous THF (10 mL) at 0 ℃ was added *n*-BuLi (3.2 mL, 2.5 mol/L in hexane, 8.0 mmol) dropwise. The ice bath was removed and the reaction mixture was allowed to stand at ambient temperature for 3 h and quenched with saturated NH_4Cl solution (30 mL). The mixture was stirred in the air for 15 h and diluted with ether (50 mL) and separated. The aqueous layer was extracted with ether (10 mL×3). The combined organic layers were washed with brine, dried over Na_2SO_4, concentrated, and purified via flash column chromatography on silica gel (hexane/ethyl acetate: 30/1) to provide **16a** (796 mg, 1.62 mmol, 81%) as white solid. m.p. 93—95 ℃; $[\alpha]_D^{23}$ +24 (*c* 0.980, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 3.94—3.82 (m, 1H), 3.60—3.47 (m, 1H), 1.24 (d, J=6.1 Hz, 3H), 0.87 (s, 9H), 0.78 (s, 3H), 0.67 (s, 3H), 0.04 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 72.3, 67.3, 61.7, 55.7, 54.5, 45.2, 42.4, 39.9, 38.8, 38.5, 37.3, 35.7, 35.1, 33.4, 33.3, 32.3, 32.1, 31.3, 28.9, 26.1, 24.1, 23.1, 21.0, 18.4, 14.4, 13.9, 12.5, –4.4; IR (KBr film) *v*: 3334, 2928, 2855, 1458, 1376, 1275, 1258, 1094, 1075, 765, 750 cm^{-1}; MS-ESI (*m/z*): 513.4 $[M+Na]^+$. Anal. calcd for $C_{31}H_{58}BrO_2Si$: C 75.85, H 11.91; found C 75.97, H 11.72.

16*β*-Methyl-3*β*-((*tert*-butyldimethylsilyl)oxy)-pregnane-20-one (17)

To a solution of **16** (1.008 g, 2.25 mmol) and SO_3•py complex (1.072 g, 6.74 mmol) in dry dichloromethane (20 mL) were added DMSO (1.5 mL, 22.4 mmol) and Et_3N (5.0 mL, 11.23 mmol) sequentially at 0 ℃. The mixture was allowed to stand at ambient temperature for 10 h then diluted with ether (100 mL). The organic layer was washed with water, dried over Na_2SO_4, filtered, concentrated under reduced pressure, and purified via flash column chromatography on silica gel (hexane/ethyl acetate: 10/1) to give ketone **17** (843 mg, 1.89 mmol, 84%). m.p. 171—172 ℃; $[\alpha]_D^{23}$ +30 (*c* 1.02, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 3.49—3.57 (m, 1H), 2.44—2.55 (m, 2H), 2.08 (s, 3H), 1.03 (d, J=6.4 Hz, 3H), 0.92 (s, 3H), 0.87 (s, 9H), 0.79 (s, 3H), 0.04 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 209.7, 72.1, 65.8, 55.5, 54.6, 45.1, 43.9, 39.1, 38.7, 37.3, 35.7, 35.7, 34.6, 33.4, 32.7, 32.3, 32.0, 28.8, 26.0, 20.8, 20.1, 18.3, 14.8, 12.5, –4.5; IR (KBr film) *v*: 2930, 2857, 1702, 1472, 1462, 1385, 1361, 1252, 1100, 870, 838, 773 cm^{-1}; MS-ESI (*m/z*): 469.2 $[M+Na]^+$. Anal. calcd for $C_{28}H_{50}O_2Si$: C 75.27, H 11.28; found C 75.11, H 11.56.

Syntheses of compounds 19, 20, and 21

Under argon atmosphere, to a solution of ketone **17** (5.05 g, 11.3 mmol) and HMDS (7.0 mL, 33.6 mmol) in anhydrous dichloromethane (50 mL) was added TMSI (2.4 mL, 16.9 mmol) dropwisely at ambient temperature. The resulting yellow solution was allowed to stand for 1 h and thin layer chromatography indicated complete comsumption of **17**. Water was added; the layers were separated; the aqueous layer was extracted with DCM for three times. The combined organic layers were dried over Na_2SO_4, filtered, and concentrated to yield a white solid which was used without further purification.

The crude product was dissolved in dry DCM (200 mL) and powdered NaOH (510 mg, 12.8 mmol) was added. To the resulting mixture, at 0 ℃, was added a solution of *m*CPBA (purified prior to usage, 5.00 g, 29 mmol) in dry DCM (100 mL) over 60 min. TLC indicated full conversion of starting material and a saturated aqueous solutin of Na_2SO_3 was added to quench the reaction. The layers were separated and the aqueous layer was extracted with DCM (150 mL×3). The combined organic layers were concentrated to dryness; the residue was dissolved with THF (500 mL) and treated with HCl (1 equiv., 50 mL). The reaction mixture was separated and the aqueous layer was extracted with DCM (50 mL×3). The combined layers were washed with saturated aqueous $NaHCO_3$ solution and brine, dried over Na_2SO_4, filtered, concentrated under reduced pressure, and purified via flash column chromatography on silica gel (DCM/MeOH: 100/1) to provide **19** (3.18 g, 57%), **20** (1.15 g, 21%) and **21** (770 mg, 16%). Compound **19**: m.p. 172—174 ℃; $[\alpha]_D^{24}$ +39 (*c* 0.490, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 4.46 (d, J=20.0 Hz, 1H), 4.27 (d, J=20.0 Hz, 1H), 3.58—3.42 (m, 1H), 1.05 (d, J=6.7 Hz, 3H), 0.83 (s, 9H), 0.79 (s, 3H), 0.76 (s, 3H), 0.00 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 212.4, 90.2, 72.2, 68.8, 54.1, 50.5, 50.3, 49.3, 45.2, 38.8, 37.3, 35.7, 35.3, 32.5, 32.0, 32.0, 28.8, 26.1, 20.7, 19.8, 18.4, 15.4, 12.5, –4.4; MS-ESI (*m/z*): 501.4 $[M+Na]^+$; IR (KBr film) *v*: 3436, 2929, 2859, 1703, 1472, 1450, 1387, 1252, 1102, 1087, 869, 838, 774 cm^{-1}. Anal. calcd for $C_{28}H_{50}O_4Si$: C 70.24, H 10.53; found C 70.54, H 10.34. Compound **20**: m.p. 191—193 ℃; $[\alpha]_D^{23}$ +14 (*c* 1.01, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 3.67—3.42 (m, 1H), 2.23 (s, 3H), 1.15 (d, J=7.1 Hz, 3H), 0.87 (s, 9H), 0.87 (s, 3H), 0.79 (s, 3H), 0.03 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 211.3, 90.9, 72.2, 54.1, 50.0, 49.5, 46.9, 45.1, 38.8, 37.3, 35.7, 35.4, 35.1, 32.4, 32.0, 31.8, 30.4, 28.8, 26.1, 20.6, 20.4, 18.4, 16.0, 12.5, –4.4; IR (KBr film) *v*: 3567, 2929, 2858, 2823, 1698, 1472, 1449, 1386, 1251, 1100, 1069, 871, 836, 775 cm^{-1}; MS-ESI (*m/z*): 485.3 $[M+Na]^+$; HRMS-ESI (*m/z*): calcd for $C_{38}H_{52}O_2SiNa^+$: 485.3421, found 485.3437. Compound **21**: m.p. 144—145 ℃; $[\alpha]_D^{23}$ +54 (*c* 1.02, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 3.62—3.44 (m, 1H), 1.17 (d, J=6.9 Hz, 3H), 0.86 (s, 9H), 0.81 (s, 3H), 0.79 (s, 3H), 0.03 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 223.6, 72.1, 54.9, 50.2, 48.3, 45.2, 43.8, 38.8, 37.3, 35.8, 34.8, 32.2, 32.0, 31.3, 31.0, 28.6, 26.1, 20.6, 18.3, 17.1, 14.3, 12.5, –4.4; IR (KBr film) *v*: 2929, 2854, 1736, 1473, 1450, 1250, 1131, 1086, 1061, 871, 841, 774, 670 cm^{-1}; MS-ESI (*m/z*): 441.3 $[M+Na]^+$; HRMS-ESI (*m/z*): calcd for $C_{26}H_{46}O_2SiNa^+$: 441.3159, found 441.3165.

16*β*-Methyl-17*α*-hydroxyl-21-acetoxyl-3*β*-((*tert*-butyldimethylsilyl)oxy)-pregnane-20-one

To a solution of **19** (155 mg, 0.32 mmol) in dry DCM/THF (4 mL/1 mL) were added DMAP (26 mg, 0.21 mmol), Ac_2O (0.13 mL, 1.38 mmol), and Et_3N (0.22 mL, 1.58 mmol). The reaction was allowed to stand at ambient temperature for 1.5 h and quenched with water. The mixture was diluted with DCM (30 mL), washed with brine, dried over Na_2SO_4, filtered, and concentrated. The residue was purified via flash column chromatography on silica gel (hexane/ethyl acetate: 10/1) to give the title compound (161 mg, 95%) as a white solid. m.p. 175−176 ℃; $[\alpha]_D^{23}$ +49 (*c* 1.02, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) *δ*: 4.97 (d, *J*=17.7 Hz, 1H), 4.86 (d, *J*=17.7 Hz, 1H), 3.63−3.40 (m, 1H), 2.18 (s, 1H), 2.15 (s, 3H), 2.08−1.92 (m, 2H), 1.09 (d, *J*=6.9 Hz, 3H), 0.86 (s, 9H), 0.78 (s, 3H), 0.78 (s, 3H), 0.03 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) *δ*: 205.3, 170.8, 90.2, 72.2, 69.6, 54.1, 50.2, 50.0, 49.2, 45.1, 38.7, 37.3, 35.7, 35.3, 35.2, 32.5, 32.0, 31.7, 29.8, 28.8, 26.1, 20.7, 19.8, 18.3, 15.0, 12.5, –4.4; IR (KBr film) *v*: 3510, 2929, 2858, 1739, 1720, 1471, 1409, 1375, 1259, 1104, 837, 841, 773, 669 cm^{-1}; MS-ESI (*m/z*): 543.2 $[M+Na]^+$; HRMS-ESI (*m/z*): calcd for $C_{30}H_{52}O_5Si\ Na^+$: 543.3476, found543.3476.

16*β*-Methyl-3*β*,17*α*-dihydroxyl-21-acetoxyl-pregnane-20-one (2)

A solution of product of the previous step (20 mg, 0.038 mmol) in THF (1 mL) was treated with HCl solution (1 equiv. 0.5 mL) at ambient temperature for 4 h, then diluted with DCM (20 mL), separated, and dried over Na_2SO_4. Concentration and purification of the residue via flash column chromatography on silica gel (hexane/acetone: 3/1) provided **2** (14 mg, 90%) as a white solid. m.p. 205−207 ℃; ^{1}H NMR (400 MHz, $CDCl_3$) *δ*: 4.98 (d, *J*=17.7 Hz, 1H), 4.87 (d, *J*=17.7 Hz, 1H), 3.67−3.51 (m, 1H), 2.16 (s, 3H), 1.11 (d, *J*=6.7 Hz, 3H), 0.80 (s, 3H), 0.80 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) *δ*: 205.2, 170.8, 90.3, 71.4, 69.6, 54.0, 50.2, 50.0, 49.3, 45.0, 38.2, 37.1, 35.7, 35.3, 32.5, 31.7, 31.6, 28.7, 20.8, 20.8, 19.8, 15.1, 12.5; IR (KBr film) *v*: 3527, 3361, 2986, 2935, 2856, 1752, 1723, 1455, 1369, 1231, 1033, 906, 782, 637 cm^{-1}; MS-ESI (*m/z*): 429.3 $[M+Na]^+$; HRMS-ESI (*m/z*): calcd for $C_{24}H_{38}O_5Na^+$: 429.2611, found 429.2616.

Results and Discussion

Because the hydroxyl groups of **11** were designed to bear different missions in the synthesis, selective transformations were necessary. Our pevious study showed that the C3-OH could be selectively protected as silyl ether in the presence of the C20-OH.[5a] Bromination-acetylation of pregnanetriol **11**, a reaction we developed previously,[5b] gave C16*α*-bromo species which provided an ideal handle for introducing methyl group.

Bromide **14** was prepared in good yield through bromination-acetylation of **11** and sequential hydrolysis of acetates in **13**. Sceening the protecting groups revealed that silyl ethers (TBS and TBDPS) are superior to alkyl ethers and esters in selective protection of the C3-OH in **14**, and that the TBS ether of **14** is a crystallizable solid whereas its TBDPS ether is a foam. Therefore, **15** was prepared from **14** in nearly quantitative yield.

We also optimized the experimental procedure. Instead of proceeding in 35% HBr/HOAc solution, the reaction was carried out in toluene with minimized dosage of HBr/HOAc. Since the acetylation of the C3-OH is much slower than the bromination-acetylation of the 1,3-diol unit, the reaction was quenched with an aqueous sodium acetate solution as soon as **11** disappeared (*ca*. 1 h, the C3-OH was partly acetylated). Evaporation of toluene ensured the removal of HOAc from the residue, therefore, hydrolysis underwent smoothly. After routine *O*-silylation, recrystallization from hexane gave **15** in 60% yield from **11** on the 150 g scale.

With **15** in hand, we then investigated its reactivity toward methyl nucleophiles (Table 1). Treating **15** with methyl magnesium chloride at ambient temperature only gave a small amount of debromination product and recovered most of the starting material (Entry 1). Same result was observed when CuBr•Me_2S was added (Entry 2). Pleasingly, the substitution occurred when dimethylcopperlithium was used (Entry 3). Lowering the amount of reagent to 1.1−1.5 equiv. and elevating the temperature to 0 ℃ provided the same results. The reaction was smoothly carried out on the 20 g scale to give **16** in excellent yield. A butyl group was also introduced by treating **15** with dibutylcopperlithium, giving **16a** in 81% yield on the gram scale (Entry 6).

Table 1 Introducing C16*β*-Me via substitution

Entry	Condition	Result
1	MeMgCl, THF, r.t. 24 h	<30% debromination (recovered **15**)
2	2.2 equiv. MeMgCl, 0 to 1.1 equiv. CuBr•Me_2S, THF, r.t., 24 h	<30% debromination (recovered **15**)
3	3 equiv. Me_2CuLi, THF, −78 ℃ to r.t., 6 h	96% **16**
4	1.1 to 1.5 equiv. Me_2CuLi, THF, 0 ℃ to r.t., 5 h	>95% **16**
5	Me_2CuLi, THF, r.t., 5 h (20 g scale)	99% **16**
6	*n*-Bu_2CuLi, THF, r.t., 20 min	81% **16a**

With the C16*β*-Me being successfully installed, attention was turned to the introduction of the required C17*α*- and C21-OHs. Nakamura and Kuwajima have reported that a double hydroxylation of silyl enol ethers with *m*CPBA gives *α*,*α*′-dihydroxyl ketones from methyl *sec*-alkyl ketones in good yields.[7] Since this

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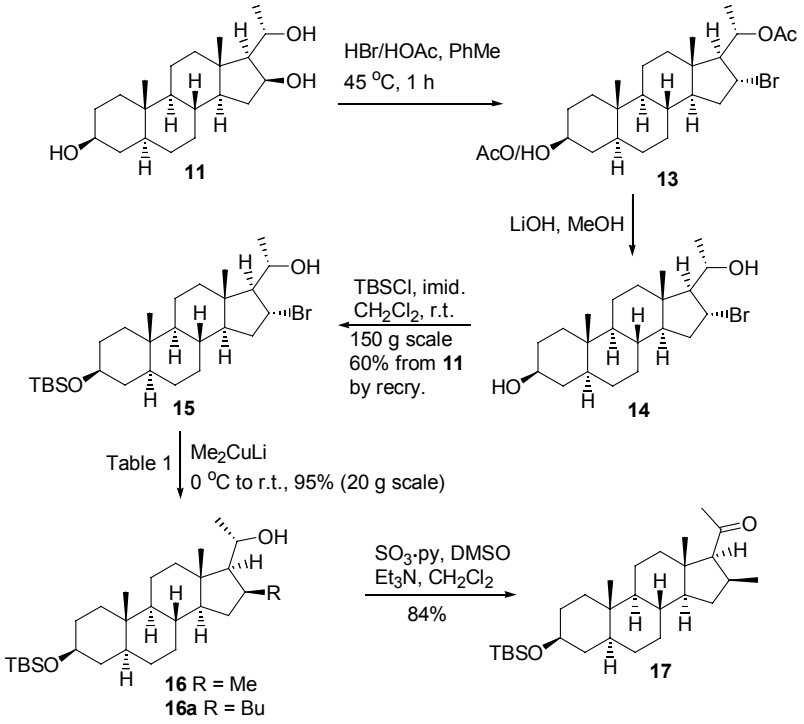
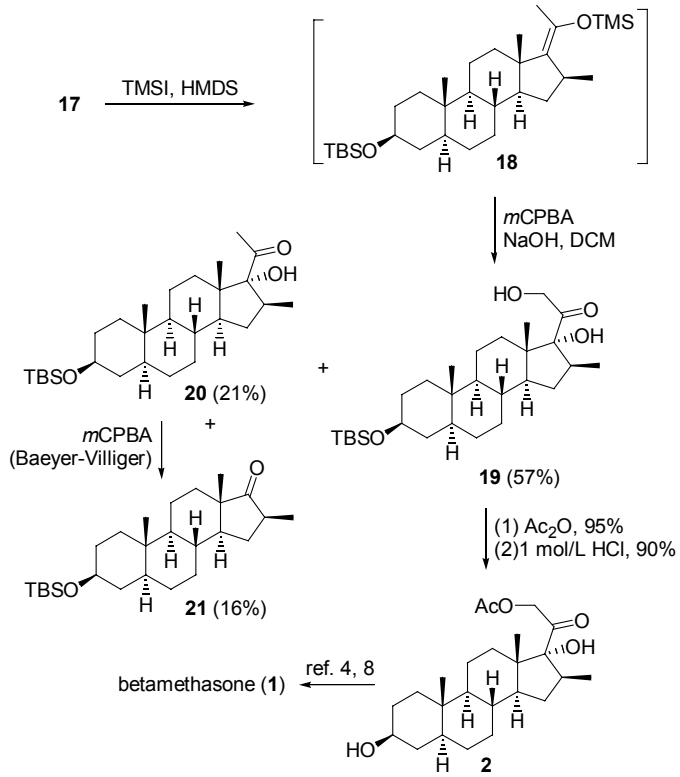
Scheme 2 Introduction of C16β-Me



Scheme 3 Oxidation to introduce OHs at C17 and C21



reaction has been used in the synthesis of dexamethasone,[7a,7c] a glucocorticoid drug and the C16-epimer of betamethasone, it was expected that the reaction is applicable to our substrate.

Pariksh-Doering oxidation of **16** provided the ketone **17** in good yield. Its silyl enol ether **18** was prepared easily by treating **17** with iodotrimethylsilane in the presence of hexamethyldisilazane and subjected to the reported conditions (2.4 equiv. *m*CPBA, 10 equiv. $KHCO_3$, CH_2Cl_2, 0 ℃). Gladly, the desired **19** was generated, but disappointedly, it was isolated only in 42% yield, along with the *mono*-epoxidized product **20**

in 11% yield and the over-oxidized product **21** in 34% yield, even after optimizing the addition rate of *m*CPBA, the reaction concentration, and the solvent. Finally, using NaOH as base gave **19** slightly better yield (57%) and reduced the formation of **21** (16%). Because no over-oxidation was observed when the reaction was performed on substrates with the C16α-Me, a result reported by Nakamura and Kuwajima[7a,7c] and repeated by us, the crowdedness of the β-face of ring D, we assumed, might facilitate Baeyer-Villiger oxidation of the C20-ketone in **19** or **20** to give ketone **21**. However, no further investigation was performed on this reaction.

The C21-OH of **21** was acetylated and the TBS ether was removed with diluted HCl aqueous to furnish **2** in high yield. Since the modifications of the ring A[8] and ring C[3c-f,4] have been previously reported, our synthesis of **2** constituted a formal synthesis of betamethasone (**1**).

Conclusions

We have accomplished a formal synthesis of betamethasone featuring a substitution strategy to introduce C16β-methyl group and a double hydroxylation to prepare the dihydroxyacetone side chain. Our method would allow the syntheses of various C16β-alkyl-substituted steroids under mild conditions. Although the unexpected over-oxidation in double hydroxylation step lowered the efficiency in establishing side chain functionalities, our method is still the shortest and most high-yielding one. Currently, using pregnanetriol in the syntheses of more drugs and natural products is ongoing in our group.

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