Cobalt-mediated Synthesis of Highly Crowded Steroids: Unusual Observations of Hindered Rotation of a Trimethylsilyl Group

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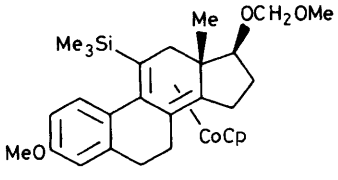
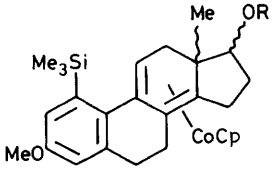
$(\eta^5\text{-}C_5H_5)Co(CO)_2$ catalyses the [2 + 2 +2] cycloaddition of silylated enediynes to furnish 1-trimethylsilyl and 1,11-bis(trimethylsilylated) A-ring aromatic steroids which exhibit unexpected hindered rotation of the trimethylsilyl groups.

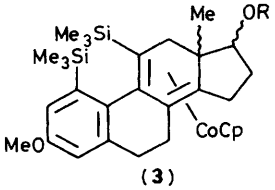
We recently reported the efficient cobalt-mediated synthesis of the steroid complex (**1**) in which the trimethylsilyl group exhibited unprecedented hindered rotation whereas the free ligand did not show this phenomenon.[1] In order to explore further the scope of this reaction and the steric effects which govern the reduced mobility of the 11-substituent we decided to modify our synthetic scheme to make accessible the 1-trimethylsilyl and 1,11-bis(trimethylsilyl) derivatives of (**1**), namely (**2**) and (**3**), and thereby to discover whether the catalyst would tolerate the construction of a highly hindered product such as (**3**) and (**2**), and whether similar hindered rotation effects would be observable.



(**1**)



(**2**)

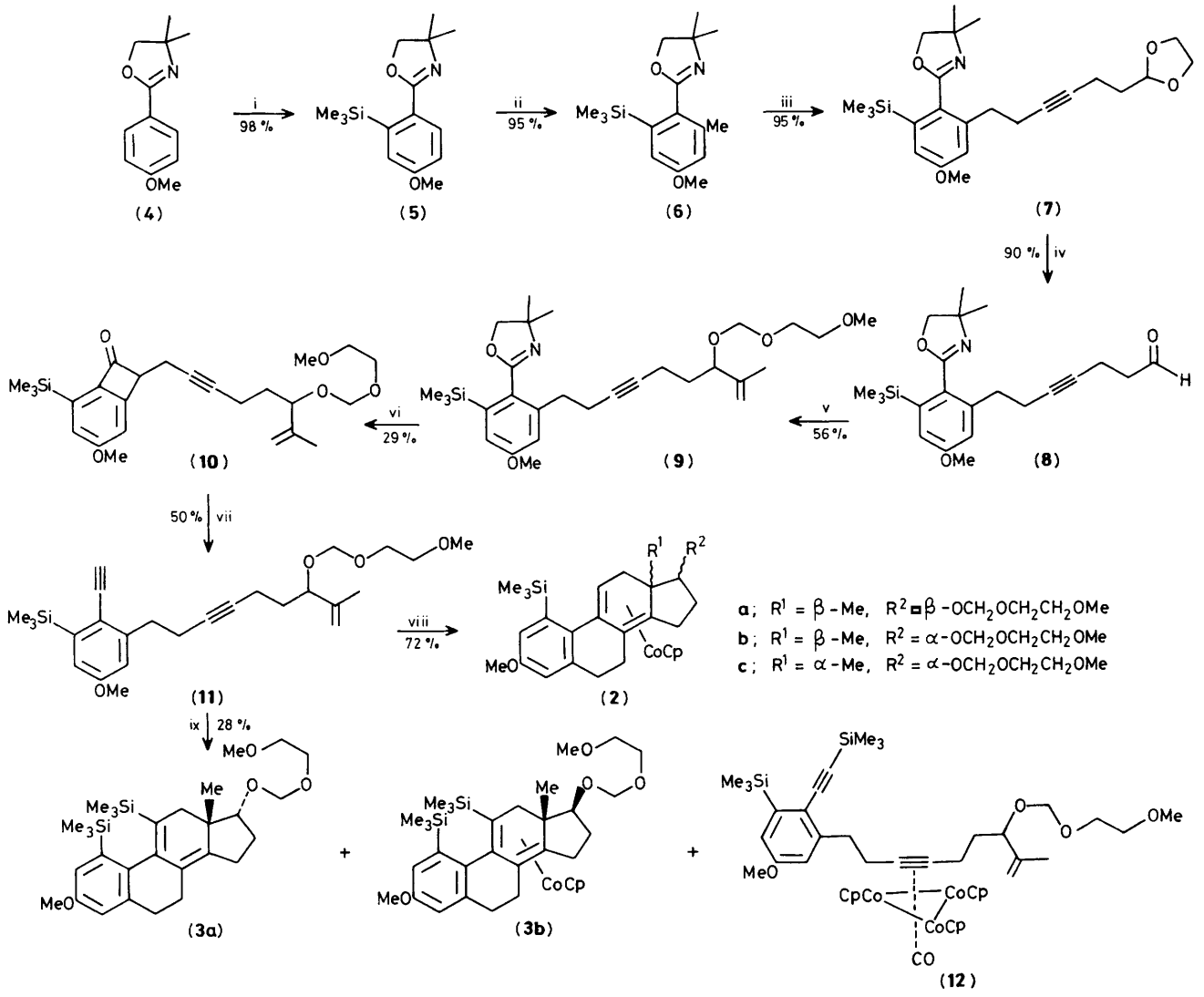


(**3**)

Cp = $\eta^5\text{-}C_5H_5$

Scheme 1 summarizes our synthetic approach patterned after the original synthesis of (**1**).† Unusual is the ring closure that occurs to give (**10**) on methylation of (**9**) followed by

† All new compounds were fully characterized. For example, compound (**2a**): m.p. 82 °C; i.r. ($CHCl_3$), 2958, 2943, 2893, 1592, 1464, 1434, 1394, 1297, 1266, 1252, 1132, 1111, 1094, and 1052 cm^{-1}; ^1H n.m.r. (300 MHz, C_6D_6), δ 0.38 (s, 9H), 0.92 (s, 3H), 1.30—1.46 (m, 2H), 1.57 (d of d, *J* 15, 4 Hz, 1H), 1.73—1.81 (m, 2H), 2.08—2.12 (m, 1H), 2.22—2.36 (m, 2H), 2.41 (d of d, *J* 15, 4 Hz, 1H), 2.85 (d of d of d, *J* 15, 2 Hz, 1H), 3.20 (s, 3H), 3.43—3.49 (m, 2H), 3.46 (s, 3H), 3.52 (t, *J* 3 Hz, 1H), 3.65—3.78 (m, 2H), 4.35 (s, 5H), 4.81 (t, *J* 8 Hz, 1H), 4.83 (s, 3H), 6.81 (d, *J* 2.5 Hz, 1H), and 7.23 (d, *J* 2.5 Hz, 1H); *M* 566.2261 (calc. 566.2251); (**2b**): m.p. 74—79 °C; ^1H n.m.r. (300 MHz, C_6D_6), δ 0.40 (s, 9H), 0.66 (s, 3H), 1.33 (d of d, *J* 15, 2.5 Hz, 1H), 1.54—1.60 (m, 2H), 1.96—2.41 (m, 5H), 2.92 (m, 2H), 3.17 (s, 3H), 3.41—3.46 (m, 2H), 3.47 (s, 3H), 3.65 (d of d, *J* 6, 2 Hz, 1H), 3.68 (t, *J* 2.5 Hz, 1H), 3.72—3.78 (m, 2H), 4.45 (s, 5H), 4.78 (d, *J* 6.7 Hz, 1H), 4.95 (d, *J* 6.7 Hz, 1H), 6.81 (d, *J* 2.4 Hz, 1H), and 7.25 (d, *J* 2.4 Hz, 1H); *M* 566.2251; (**3b**): i.r. (CCl_4), 2959, 2942, 2898, 2841, 1588, 1469, 1414, 1339, 1300, 1251, 1148, 1113, 1097, and 1047 cm^{-1}; ^1H n.m.r. (300 MHz, $CDCl_3$), δ 0.00 (s, 9H), 0.11 (s, 9H), 0.68 (s, 3H), 1.01 (d, *J* 15 Hz, 1H), 1.51—1.84 (m, 4H), 2.07 (d, *J* 15 Hz, 1H), 2.26 (m, 2H), 2.40 (m, 1H), 2.89 (d of d of d, *J* 15, 5, 2 Hz, 1H), 3.46 (s, 3H), 3.64—3.81 (m, 5H), 3.83 (s, 3H), 4.48 (s, 5H), 4.86 (d, *J* 14.5 Hz, 1H), 4.92 (d, *J* 14.5 Hz, 1H), 6.64 (d, *J* 2.2 Hz, 1H), and 6.84 (d, *J* 2.2 Hz, 1H); *M* 638.2644 (calc. 638.2644); (**12**): i.r. ($CHCl_3$), 2965, 2898, 2142, 1707, 1587, 1462, 1416, 1251, 1094, 1039, and 1019 cm^{-1}; ^1H n.m.r. (300 MHz, $CDCl_3$), δ 0.23 (s, 9H), 0.42 (s, 9H), 1.41—1.73 (m, 2H), 1.80 (s, 3H), 2.18—2.41 (m, 2H), 3.02—3.29 (m, 4H), 3.35 (s, 3H), 3.38—3.55 (m, 4H), 3.88 (s, 3H), 4.28 (t, *J* 8 Hz, 1H), 4.65 (s, 15H), 4.74 (d, *J* 18 Hz, 1H), 4.79 (d, *J* 18 Hz, 1H), 5.03 (br. s, 1H), 5.08 (br. s, 1H), and 6.95 (br. s, 2H); *M* 914.2043 (calc. 914.2037).



Scheme 1. i, a, Bu^nLi, 0 °C, ether, b, Me_3SiCl; ii, a, Bu^nLi, 0 °C, ether, MeI; iii, a, Bu^nLi, 0 °C, ether, b, $BrCH_2C{\equiv}CCH_2CH_2CH(OCH_2CH_2O)$, hexamethylphosphoric triamide; iv, HCO_2H; v, a, $CH_2{=}CH(Me)MgBr$, b, $Et_3N^+CH_2OCH_2CH_2OMeCl^-$; vi, a, MeI, b, MeMgCl, c, HCl, MeOH; vii, a, MeMgCl, b, $Bu^tO^-K^+$, c, PCl_5–pyridine; viii, $(\eta^5\text{-}C_5H_5)Co(CO)_2$; ix, a, Bu^nLi, Me_3SiCl, b, $(\eta^5\text{-}C_5H_5)Co(CO)_2$.

treatment with MeMgCl, meant to provide the acetophenone.[1] However, the benzocyclobutenone (**10**) could be methylated, ring-opened, and eventually converted into (**11**) by employing PCl_5–pyridine.[2] Cobalt-mediated [2 + 2 + 2] cyclization[3] of (**11**) gave three products (**2a**—**c**)† in 31, 18, and 23% yield, respectively, and with surprising lack of stereoselectivity. The stereochemistry in these products was assigned by comparison of the highly characteristic n.m.r. spectra with those of (**1**) and related model compounds[1,3,4] (two of which were characterized by *X*-ray analysis),[1] decoupling, and nuclear Overhauser enhancement experiments. Remarkably, despite the seeming close structural similarity of (**2**) and (**1**), none of these complexes exhibited hindered rotation of the trimethylsilyl group on the ^1H n.m.r. time-scale (300 MHz, −60 °C).

Consequently, (**11**) was silylated and subjected to the cyclization conditions. The reaction was sluggish furnishing unchanged starting material (10%) after 8 h (boiling *m*-xylene, *hν*, GE-ELH 300W projector lamp) in addition to the steroid (**3a**) (9%), complex (**3b**) (10%), the unusual cluster (**12**) (9%)† (to our knowledge the first cobalt complex of its kind),[5] separated by h.p.l.c., and other unidentified products. The outcome of this reaction demonstrates once again the unique ability of the catalyst to assemble highly hindered systems.[3] Surprisingly, the trimethylsilyl groups in (**3a**) do not exhibit hindered rotation, although the strained nature of this compound is evident by its unexpected air sensitivity which leads to the rapid uptake of O_2 (mass spectrum) and decomposition, an observation made earlier for this chromophore in a nonsilylated derivative,[4] but not for the free ligand in (**1**) which is stable. In contrast, the (stable) complex (**3b**) has a temperature-dependent ^1H n.m.r. spectrum. At −90 °C one of the two trimethylsilyl singlets splits into three sharp lines at δ 0.21, 0.06, and −0.65, revealing hindered rotation. The other trimethylsilyl peak remains sharp throughout. A temperature dependence study and computer simulation[6] gave the following activation parameters: $\Delta G^{\ddagger}_{293} = 11.7(0.12)$ kcal mol^{-1}, $\Delta H^{\ddagger} = 9.6(0.46)$ kcal

mol^{-1}, $\Delta S^{\ddagger}$ = 6.7(1.85) cal mol^{-1} K^{-1} (1 cal = 4.184 J). These figures should be compared with those for (**1**): $\Delta G^{\ddagger}$ = 16.8 kcal mol^{-1}, $\Delta H^{\ddagger}$ = 18.8 kcal mol^{-1}, and $\Delta S^{\ddagger}$ 6.7 cal mol^{-1} K^{-1}. Thus, the formally much more highly strained (**3b**) shows less hindrance to rotation of the trimethylsilyl group than (**1**) (perhaps indicative of non-cogwell pathways for this movement[7]).

Based on this and earlier results,[1] we suggest that it is the trimethylsilyl group located on the complexed diene unit which gives rise to this observation. It appears that metal complexation is necessary (or at least serves to amplify) the effect of hindered rotation in these systems and that this effect is highly dependent on the exact structural and electronic arrangement around the metal [which must differ substantially in the two systems (**1**) and (**3b**)]. It is possible that some type of electronic effect involving silicon orbitals[8] in conjunction with steric encumbrance is responsible for this unusual behaviour. Clarification of that point will have to await the outcome of further structural and dynamic studies.

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