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A SHORT, SIMPLE, STEREOCONTROLLED, STEROID TOTAL SYNTHESIS: (±)-11-OXOEQUILENIN METHYL ETHER

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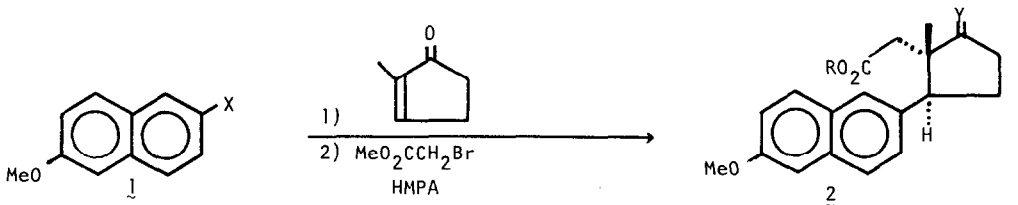
Steroids are vitally involved in normal regulation of many human physiological functions.[1] Many partially and totally synthetic steroids are produced industrially for use as drugs.[2] Two of the most challenging problems in devising new syntheses of steroids are control of stereochemistry[3] and efficiency in construction of the tetracyclic carbon skeleton. We report here a new steroid synthesis in which control of relative stereochemistry is virtually complete and in which a usefully-functionalized steroid is produced expeditiously in only four steps from readily available starting materials. Our general and convergent[4] synthetic plan involved joining aromatic rings A-B to ring D and then forming ring C *via* a Friedel-Crafts cyclization (AB+D→ABD→ABCD[5]).

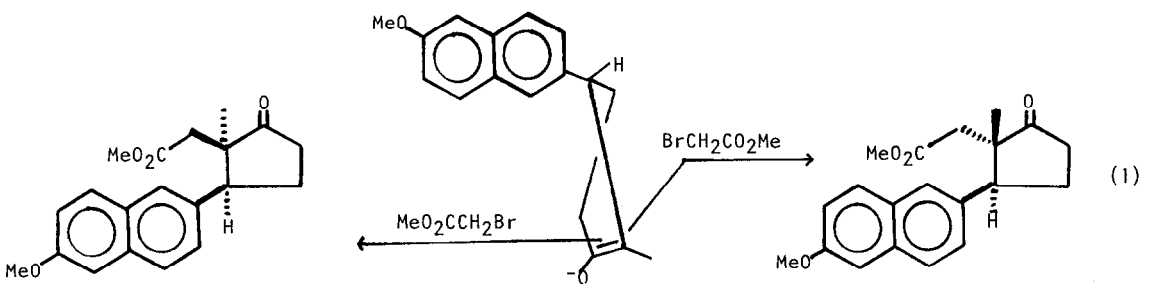
6-Methoxy-2-bromonaphthalene (1a)[6] was converted into 6-methoxy-2-naphthyllithium (1b, *n*-butyllithium in diethyl ether[7], -25°, 30 min) and then into 6-methoxy-2-naphthyl(1-pentynyl)copperlithium (1c, 1-pentynylcopper[8] in ether, -5°, 30 min). Reaction of one equivalent of this naphthylcopperlithium reagent with one equivalent of 2-methylcyclopentenone[9] (ether, 0°, 4 hrs) generated a dark green suspension which was added *via* syringe to a 0° solution of methyl bromoacetate and hexamethylphosphoric triamide (1:3 ratio)[10]. After 18 hrs of stirring at ambient temperature, tricyclic keto ester 2a was isolated and, without purification, was converted into ketal ester 2b (ethylene glycol, catalytic *p*-toluenesulfonic acid, benzene reflux, 12 hrs, Dean-Stark trap) which was saponified (KOH, MeOH reflux, 6 hrs; aqueous $NaHCO_3$ and Et_2O at 0°; conc. HCl until neutral) to form ketal acid 2c.[11] One recrystallization (benzene/cyclohexane) gave pure ketal acid 2c in 48% overall yield, mp. 175-178°. Likewise pure keto acid 2d[12] was prepared by saponification of crude keto ester 2a and was recrystallized in 57% overall yield, mp. 153.0-154.0° (lit. mp 153.5-154.5°[13] ; 154°[14]).



1a, X = Br
1b, X = Li
1c, X = (CuC≡CPr-n)Li

2a, R = Me, Y = O
2b, R = Me, Y = OCH_2CH_2O
2c, R = H, Y = OCH_2CH_2O
2d, R = H, Y = O

The remarkable stereochemical purity of steroid intermediates 2a-2d was established by proton nmr spectroscopy as had been done before for AB-aromatic 9,11-seco steroids.[15] For example, the 18-methyl singlet of keto acid 2d had been reported to occur at δ0.68, whereas that of iso-2d [cis-2-(6-methoxy-2-naphthyl)-1-methyl-5-oxocyclopentane-r-1-acetic acid] had been recorded at δ1.33.[15a] In the nmr spectrum of our synthetic crude and recrystallized keto acid 2d, there was a strong singlet at δ0.68 but there was no signal discernible at δ1.30-1.35; by expanded nmr integration we placed an upper limit of 0.5% on the amount of iso-2d that could possibly have been present. Likewise, proton nmr of the crude tricycles 2a-2c showed no detectable methyl singlet in the range δ1.15-1.35 characteristic of a cis-2-methyl-3-naphthylcyclopentanone, which indicated that 9,11-seco steroids 2a-2c were stereochemically pure. A reasonable explanation for this virtually complete stereocontrol is pictured in eq. 1.

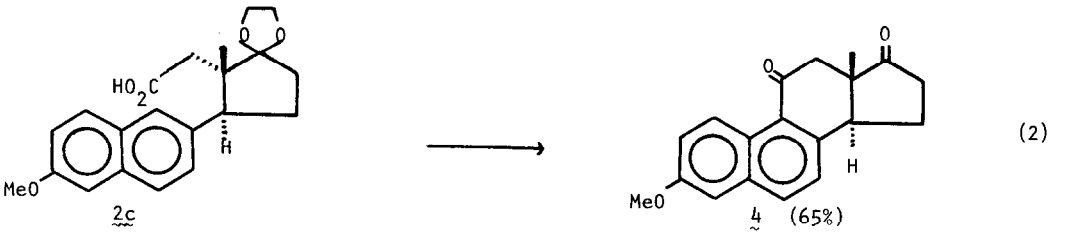


(1)

iso-2a 3 2a

Approach of the bromoacetate electrophile toward the more hindered β-face of cyclopentanone enolate 3 appears to be sterically less favorable than approach toward the less obstructed α-face (steric approach control), and iso-2a having the methoxycarbonylmethyl group cis to the naphthyl group is probably less stable than 2a having the smaller methyl group cis to the naphthyl group (product development control).[16] Steric approach and product development factors, therefore, both operate in the same direction, and the synergistic effect of these two factors may be the basis for the observed, essentially complete, stereocontrol in formation of 2,2,3-trisubstituted cyclopentanone 2a having the natural steroid relative stereochemistry at the incipient C,D-ring fusion. In contrast, Vollhardt has found much lower stereocontrol in alkylation of an enolate similar to 3 but with the small vinyl group in place of the large methoxynaphthyl group.[17,18]

Cyclization of ketal acid 2c (anhydrous HF, -78° and then ambient temperature, 14 hrs; aqueous $NaHCO_3/Et_2O$) produced chemically and stereochemically pure (±)-11-oxoequilenin methyl ether (4, eq. 2) in 65% yield after one recrystallization (benzene/petroleum ether, mp 220.5-222.0° (lit mp 218-221°,[19] 222-224°[14]))[20]. Proton nmr analysis showed an 18-methyl singlet at δ0.8 for C,D-trans steroid 4 and no absorption whatsoever at δ1.2 characteristic of C,D-cis 11-oxoisoequilenin methyl ether.[15a] Acid promoted cyclization of keto-acid 2d to form trans-1-hydrindanone 4 was not very successful as had been noted previously.[21,22] The reasons for the ease of cyclization of ketal-acid 2c but the difficulty of cyclization of keto-acid 2d are unclear at this time. This is the first report of a high-yield Friedel-Crafts cyclization of a trans-3-aryl-2-carboxymethylcyclopentanone into a trans-1-hydrindanone.[21-23]



(2)

The total yield of recrystallized equilenin 4 over four steps, without chromatography, and based on readily available 2-methylcyclopentenone or on 6-methoxy-2-bromonaphthalene was 31% (65x48). The stereochemical purity of equilenin 4 produced in this way was at least 99.5%. This is one of the most efficient and stereocontrolled steroid total syntheses ever reported. The 3,11, 17-oxygenation pattern in equilenin 4 affords numerous possibilities for further transformations leading to other steroids. 11-Oxoequilenin methyl ether (4) has been converted previously into various A-ring aromatic (e.g., estrone)[22] and non-aromatic (e.g., norethisterone) steroids of contraceptive value.[1b] We are currently exploring application of our new synthetic methodology to preparation of optically active and structurally modified steroids.

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9. Prepared according to the general method of W. F. Gannon and H. O. House, "Organic Syntheses", Coll. Vol. J. Wiley, New York, N.Y., 1973, p. 294.

10. We thank Professor Martin Semmelhack (Cornell University) for informing us of this inverse addition procedure before publication.

11. 2a: purified by preparative tlc ($CHCl_3$) R_f=0.35; colorless oil; m/e (rel. intensity): 326 (M^+, 80), 253 (100); nmr (100 MHz) ($CDCl_3$) δ3.82 (S, 3H, $ArOCH_3$), 3.64 (S, 3H, - $COOCH_3$), 0.62 (S, 3H, 18-CH_3); ir(film) 1745 and 1737 cm^{-1};

2b: purified by preparative tlc (10% EtOAc:benzene) R_f=0.35; colorless oil; m/e (rel. intensity): 370 (M^+, 50), 297(100); nmr (100 MHz) ($CDCl_3$) δ3.82 (S, 3H, $ArOCH_3$), 3.80 and 3.62 (4H, -OCH_2CH_2O-), 3.54 (S, 3H, $COOCH_3$), 0.90 (S, 3H, 18-CH_3); ir (CCl_4) 1732, 1170 cm^{-1};

2c: nmr (100 MHz) ($CDCl_3$) δ4.0 (broad S, 4H, -OCH_2CH_2O), 3.82 (S, 3H, $ArOCH_3$); 0.90 (S, 3H, 18-CH_3); ir($CHCl_3$) 3520, 3040, 2945, 1700, 1725, 1150 cm^{-1}.

12. 2d: nmr (100 MHz) ($CDCl_3$) δ9.8 (M, 1H, COOH), 7.65 (T, 2H), 3.90 (S, 3H, $ArOCH_3$), 0.68 (S, 3H, 18-CH_3); ir ($CHCl_3$) 2980, 2880, 1750-1700 (broad) cm^{-1}; Anal. Calcd. for $C_{19}H_{20}O_4$: C, 73.06; H, 6.45. Found: C, 73.22; H, 6.58.

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20. 4: m/e 294 (M^+); nmr (100 MHz) ($CDCl_3$) δ8.02 (D, J=9Hz, 1H), 7.60 (D, J=7Hz, 1H), 3.80 (S, 3H, $ArOCH_3$), 0.83 (S, 3H, 18-CH_3); (CD_3COCD_3) δ8.02 (D, J=9Hz, 1H), 7.2-7.4 (4H), 3.9 (S, 3H, $ArOCH_3$), 0.85 (S, 3H, 18-CH_3); ir ($CHCl_3$) cm^{-1} 2990, 2940, 2840, 1730, 1670, 1600; Uv (95% EtOH): λ_{max} (ε) 242 (24,500), 316 (4,500). These nmr, ir, and uv data correspond to those reported for steroid 4 in refs. 14, 19.

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