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A HIGHLY CONVERGENT AND FLEXIBLE STRATEGY FOR THE SYNTHESIS OF A-RING AROMATIC STEROIDS

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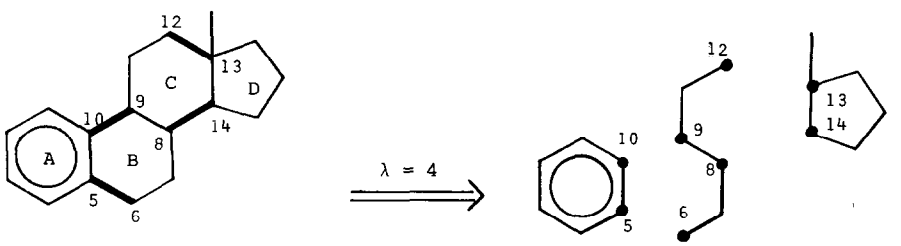
SUMMARY: Using Hendrickson's criteria for systematic synthesis design, a strategy featuring a linear six carbon synthon (7) for bis-annulation has been devised for economic, flexible and highly convergent syntheses of A-ring aromatic steroids.

New A-ring aromatic steroids continue to be prime synthetic targets[1] for potential use in fertility control, bioassays, or as antineoplastic agents.[2] By using Hendrickson's criteria for systematic synthesis design,[6] we have devised a highly convergent and essentially "self-consistent" strategy for making this class of compounds that allows great flexibility for introducing different A and D rings, and that is amenable to the incorporation of substituents into rings B and C. The strategy also leads to prochiral intermediates of the Smith-Hughes type[3,4] which can be cyclized enantioselectively to optically active steroid precursors. Here we outline the logic behind this approach and illustrate its main features by making an estrone precursor (11c),[4] and an intermediate (11f) for the preparation of an "impeded estrogen".[5]

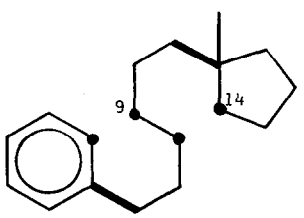
We identified in the general target molecule (1) 4 prime bonds for construction (bond set $\lambda = 4$; C5-C6, C9-C10, C8-C14, C12-C13) which maximize convergency and flexibility. This generated three hypothetical synthons (2), (3), and (4) of equal size on which functionality had to be imposed that would enable their union, ideally in a self-consistent sequence.[6]



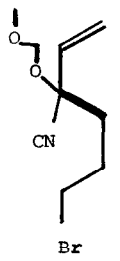
(1) (2) (3) (4)

The strategy clearly hinged upon the central structural unit (3); thus, our prime objective was to design and make a correctly functionalized linear 6 carbon synthon for bis-annulation with the indicated 4 construction sites.[6] In order to simplify the problem of designing this key synthon, we considered the consequences of affixing synthons (2) and (4)

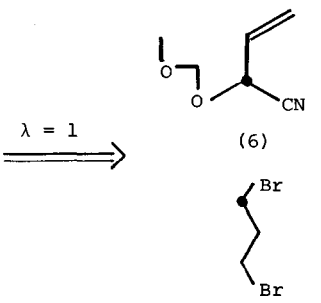
to the termini of (3) (C5+C6, C12+C13) to give a general intermediate (5) and of imposing upon this at C9 and C14, carbonyl groups (or their equivalent) to facilitate the 2 future cyclizations.[7] The functionality site-span[6] of 5 thereby introduced, immediately suggested a Michael reaction for joining synthons (3) and (4). This indicated that a potential enone was required in (3), and effectively restricted the ways of efficiently joining synthons (3) and (2) to equivalents of C-C coupling such as "reductive-alkylation" of aromatic acids[8] followed by oxidative decarboxylation.[9]



(5)



(7)

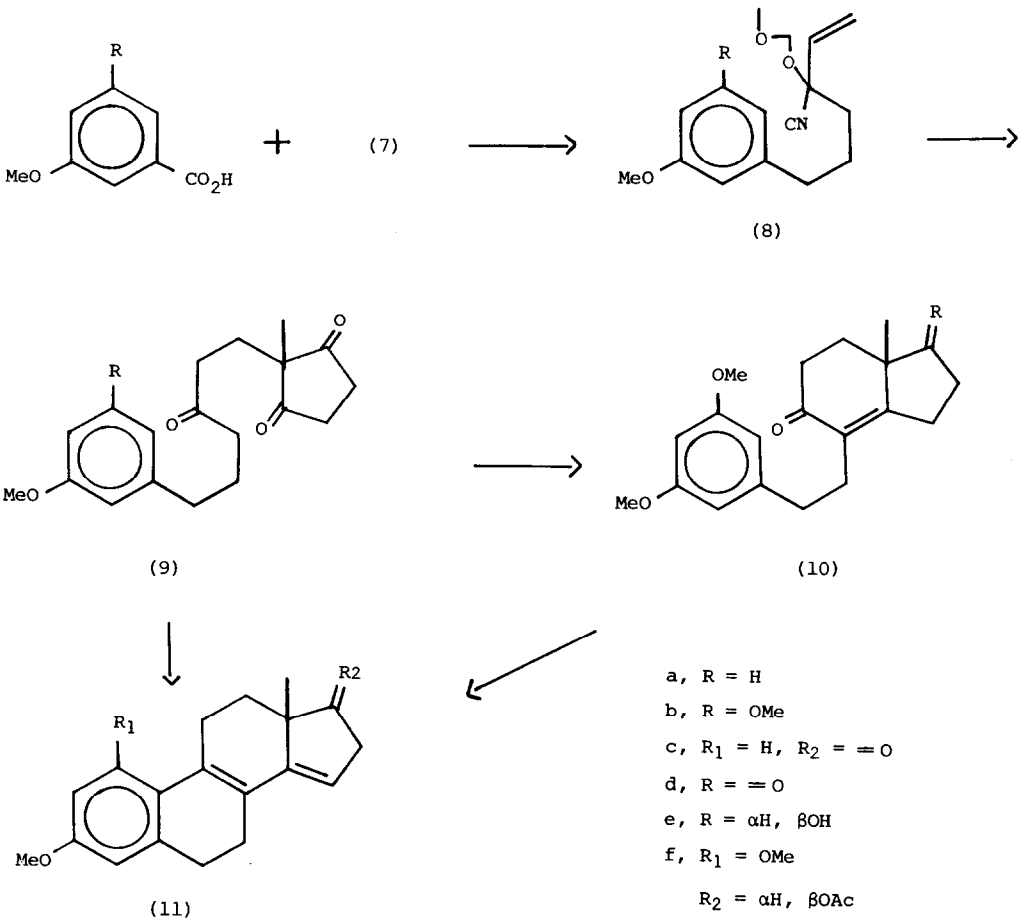


We conceived, therefore, of synthon (7), and of an economical preparation as follows: the cyanohydrin of acrolein was protected as the methoxymethyl ether (6)[10] using dimethoxymethylene, CH_2Cl_2 and P_2O_5(5°, 18h)[11] then the anion (LDA, 1.1 eq, -60°, 1h) alkylated with 1,3-dibromopropane (1.1 eq) to give (7)[10] in about 70% yield.[12] With this key synthon in hand, we then devised methods for adding future A and D rings using steroid precursors (11c and f) as convenient targets.

Grignard coupling[13] was moderately successful for affixing the A-ring, but "reductive alkylation" of an aromatic acid with (7) (1 eq), followed by anodic (C, 0.5amp, THF-H_2O 8:1 Et_3N 1.5 eq), or LTA oxidation (1 eq, Py cat, CH_2Cl_2, 0°, 15 min) was superior in terms of yield and reliability. Thus, m-methoxybenzoic acid, or veratric acid, gave the m-methoxy benzene derivative (8a)[10] in 90% yield, and the dimethoxy analogue (8b)[10] was similarly obtained from 3,5-dimethoxybenzoic acid.

In order to affix the future D-ring, the enone function in (8a and b) was unmasked through "titration" with BBr_3 in CH_2Cl_2(-78°, 10% $NaHCO_3$ quench) then reflux in THF-H_2O (8:1 N-ethylmorpholine to pH7, 1h). Although the two enones[10] could be isolated, it was more efficient to add 2-methylcyclopenta-1,3-dione (1.5 eq, Et_3N to pH7, 40°, 120h) and alkylate *in situ*. In this way the prochiral triones (9a)[4,10] and (9b)[10] were prepared in high overall yield (>92%).

For the purpose of characterization, trione (9a) was treated in refluxing benzene with H_3PO_4-P_2O_5(4:1, 45 min) to give the crystalline tetracyclic estrone precursor (11c).[4,10] Enantioselective cyclization of trione (9b) in CH_3CN-$HClO_4$ (0.25M, 0.25 eq), 9:1 (90°, 240h) containing L-phenylalanine (1.1 eq), gave the 9,10-seco-steroid (10d)[10] in 78% yield and 66% e.e.[14]



The optical yield was deduced through $NaBH_4$ (0.5 eq, EtOH, -17°, 1.5h) reduction to the 17β-ol (10e)[10] then cyclized in AcOH-Ac_2O (1:1, $HClO_4$ cat, 22°, 18h) to the target tetracyclic acetate (11f)[10] of known optical rotation.[5]

The prochiral triones (9a and b) are, of course, of the Smith-Hughes type[4] which have been cyclized enantioselectively by Eder and Danishevsky using similar procedures.[14] However, the strategy which we have developed using Hendrickson's criteria and which features the versatile six carbon synthon (7), is more convergent, flexible, and synthetically economical than pre-existing methods leading to these aromatic steroid-precursors.

References and Notes

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7. C8 + C14 through an Aldol reaction and C9 + C10 through an Ar-S_E^i process.[4]

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10. Selected data as follows: (6) bp 55°/4 mm, ^{1}H NMR ($CDCl_3$) δ 3.48 (s, 3H), 4.76 + 4.90 (ABq, J = 7Hz, 2H, OCH_2O), 4.96 (d, J = 5Hz, 1H, HCCN), 5.5 (br d, J = 10Hz, 1H) 5.85 (m, 2H). Anal. ($C_6H_9NO_2$) C, H, N. (7) bp 60°/0.01 mm, ^{1}H NMR ($CDCl_3$) δ 2.10 (m, 4H), 3.48 (s, 3H), 4.76 + 4.90 (ABq, J = 7Hz, 2H), 5.60 (m, 1H), 5.75 (m, 2H); IR (film) 2280(w), 1620(w), 1435, 1405, 1260, 1205, 1150, 1080, 1000, 920 cm^{-1}; MS m/z 217, 219 (M− CH_2O) (15%), 186, 188 (M− $C_2H_4O_2$) (35), 138 (63), 126 (M− C_3H_6Br) (100); Anal. ($C_9H_{14}NO_2Br$) C, H, N, Br. (8a) bp 65°/0.008 mm, ^{1}H NMR ($CDCl_3$) δ 1.90 (m, 4H), 2.70 (m, 2H), 3.44 (s, 3H), 3.82 (s, 3H), 4.74 + 4.88 (ABq, J = 7Hz, 2H), 5.5 (m, 1H), 5.7 (m, 2H), 6.80 (m, 3H), 7.24 (t, J = 8Hz, 1H); IR (film) 1600, 1580, 1255, 1150, 1080, 1000, 930. 770 cm^{-1}; Anal. ($C_{16}H_{21}NO_3$) C, H, N. (8a enone)[4] IR (film) 1695 (sh), 1680, 1600, 1250, 1140, 1030, 765 cm^{-1}. (8b) bp 75°/0.005 mm, ^{1}H NMR ($CDCl_3$) δ 1.9 (m, 4H), 2.60 (m, 2H), 3.40 (s, 3H), 3.72 (s, 6H), 4.66 + 4.80 (ABq, J = 7Hz, 2H), 5.44 (m, 1H), 5.66 (m, 2H), 6.30 (s, 3H); IR (film) 1600, 1200, 1150, 1000, 930, 825 cm^{-1}; Anal. ($C_{17}H_{23}NO_4$) C, H, N. (8b enone) bp 85°/0.015 mm, ^{1}H NMR ($CDCl_3$) δ 2.00 (q, 2H), 2.60 (t, 4H), 3.72 (s, 6H), 5.76 (dd, J = 2,8Hz, 1H), 6.25 (m, 5H); IR (film) 1695 (sh), 1680, 1600, 1460, 1200, 1140, 1000, 820 cm^{-1}; Anal ($C_{14}H_{18}O_3$) C, H. (9a)[4] ^{1}H NMR ($CDCl_3$) δ 1.10 (s, 3H), 1.90 (m, 4H), 2.50 (m, 6H, H_2CCO), 2.72 + 2.88, (br ABq, J = 16Hz, H_2CAr), 3.80 (s. 3H), 6.76 (m, 3H), 7.20 (t, J = 8Hz, 1H); IR (film) 1760 (sh), 1718 (br), 1600, 1250, 1150, 1140, 770, 720 cm^{-1}. (9b) ^{1}H NMR ($CDCl_3$) δ1.08 (s, 3H), 1.84 (m, 4H), 2.50 (m, 6H), 2.64 + 2.80 (br ABq, J = 16Hz, 2H), 3.80 (s, 6H), 6.02 (s, 3H); IR (film) 1755 (sh), 1720, 1600, 1200, 1145, 1050, 825 cm^{-1}; MS m/z 346 (10), 164 (100); Anal. ($C_{20}H_{26}O_5$) C,H. (10d) bp 130°/0.01 mm, $[\alpha]_D^{22}$ + 104° (0.5 $CHCl_3$, 66% ee); ^{1}H NMR ($CDCl_3$) δ 1.10 (s, 3H), 3.74 (s, 3H), 6.22 (br s, 3H); IR (film) 1740, 1660, 1600, 1200, 1140, 1050, 820 cm^{-1}; Anal. ($C_{20}H_{24}O_4$) C,H. (10e) mp 95-98°; ^{1}H NMR ($CDCl_3$) δ 1.06 (s, 3H), 3.78 (s, 3H), 6.28 (br s, 3H); IR (Nujol) 3400, 1650, 1600, 1200, 1150, 1060, 825 cm^{-1}; Anal. ($C_{20}H_{26}O_4$) C,H. (11c) mp 113-115° (lit.[4] 115-116°); ^{1}H NMR ($CDCl_3$) δ 1.10 (s, 3H), 3.92 (s, 3H), 6.00 (m, 1H), 6.88 (m, 2H), 7.40 (d, J = 10Hz, 1H); IR (Nujol) 1745, 1600, 1040, 800 cm^{-1}. (11f) mp 143-144.5°, $[\alpha]_D^{22}$ -35° (0.5 $CHCl_3$, 66% ee) (lit.[5] mp 142-143.5°, $[\alpha]_D^{RT}$ -53.6°) NMR ($CDCl_3$) δ 1.04 (s, 3H), 2.10 (s, 3H), 3.76 + 3.79 (2, 6H), 5.00 (t, J = 8Hz, 1H), 5.45 (m, 1H), 6.33 (s, 2H); IR (Nujol) 1720, 1590, 1230, 1215, 1020, 800 (w) cm^{-1}; Anal. ($C_{22}H_{26}O_4$) C,H.

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