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REGIOCONTROLLED SYNTHESIS OF THE ERGOSTEROL B-ISOMERS

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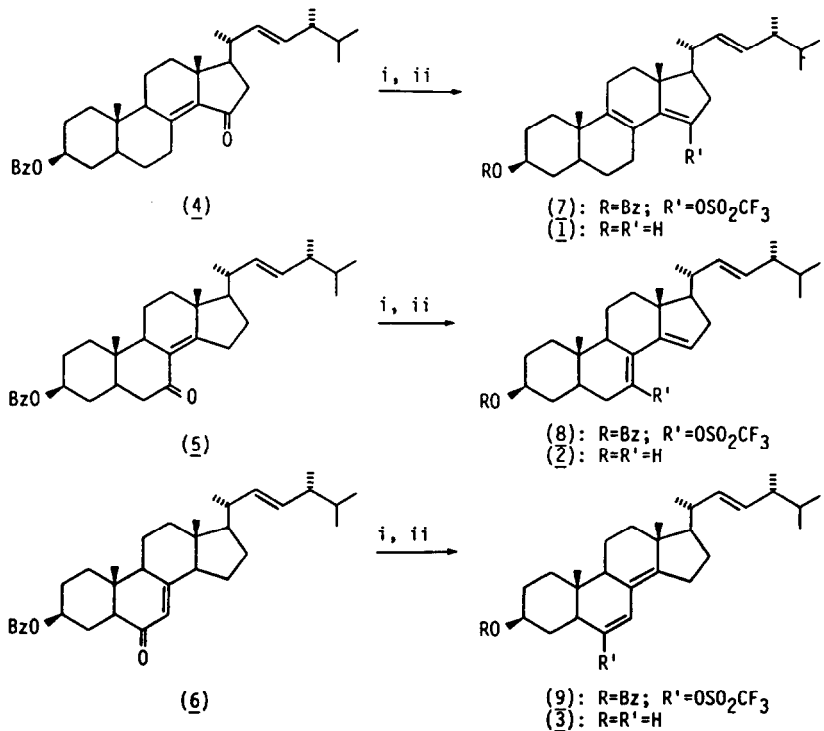
Summary: A novel, regiocontrolled synthesis of the ergosterol B-isomers, (1), (2) and (3) is described, the success of which was realized via the highly regioselective formation of intermediate trienoltriflates, (7), (8) and (9).

An intriguing problem of long standing interest in steroid chemistry is the regiospecific preparation of the ergosterol B-isomers, B_1, B_3 and B_2, identified as (3β,5α,22E)-ergosta-8,14,22-, 7,14,22-, and 6,8(14),22-trien-3-ols, (1), (2) and (3), respectively.[2,3] Some 55 years ago, in his now classic study, Windaus[2a] isolated and characterized the B-isomers following exposure of ergosterol to HCl in $CHCl_3$. Numerous investigators have since attempted to exploit the homo-nuclear-5,7-diene isomerization to generate, on demand, a single triene isomer.[3] However, it is now recognized that mixtures of the ergosterol B-isomers are always obtained under acid-catalyzed conditions.[3g] Other, more selective methods for promoting controlled isomerization are continually being sought[3f,g] in light of the importance of these sterols as synthetic and biosynthetic intermediates. A novel approach to the regiocontrolled synthesis of these trienes is described here, the success of which was dependent upon the regiospecific generation of trienoltriflates from appropriate steroid dienone precursors.

The ratio of B-isomers produced in the acid-catalyzed isomerization of ergosterol is a function of reaction conditions.[2,3] B-isomers (2) and (3) may be identified as the kinetically derived trienes of this isomerization, while triene (1) as the thermodynamic product. This suggests a relative order of thermodynamic stability for the isomeric trienes with the 8,14,22-triene, (1), being more stable than the 7,14,22-triene, (2), > 6,8(14),22-triene, (3) > 5,7,22-triene (ergosterol), an observation which has not been appreciated previously. By analogy with the stability trend for these trienes, we reasoned that reaction of enones (4),[3d] (5)[5] and (6)[5] with trifluoromethanesulfonic acid anhydride (Tf_2O) and 2,6-di-t-butyl-4-methylpyridine (DBMP) in CH_2Cl_2[4a] under thermodynamic (i.e. reversible) conditions would provide trienoltriflates (7), (8) and (9), respectively, as major products.

It was gratifying to observe that each of the dienones (4), (5) and (6) did indeed give rise to their anticipated trienoltriflates (7), (8), (9) (1.2 eq. Tf_2O, 1.4 eq. DBMP, CH_2Cl_2, 12 h, 25 °C then 30 min, reflux) with high regioselectivity (>97 %, HPLC) in essentially quantitative yield. Each triflate was smoothly reduced to the corresponding triene (12 eq. Bu_3N, 8 eq. HCOOH, 0.2 eq. $Pd(OAc)_2$, 0.4 eq. PPh_3, DMF, 30 min, 70 °C)[4b] then saponified (4 eq. NaOMe, 3:1 MeOH-toluene, 12 h, 25 °C) affording pure ergosterol B_1 (1), B_3 (2) and B_2 (3) in 75-80 % overall yield (following recrystallization from EtOAc-MeOH).



(4)

(7): R=Bz; R'=OSO_2CF_3
(1): R=R'=H

(5)

(8): R=Bz; R'=OSO_2CF_3
(2): R=R'=H

(6)

(9): R=Bz; R'=OSO_2CF_3
(3): R=R'=H

(i) Tf_2O, 2,6-di-t-butyl-4-methylpyridine, CH_2Cl_2
(ii) Bu_3N, HCOOH, $Pd(OAc)_2(Ph_3P)_2$ (cat.), DMF, then NaOMe, MeOH, toluene

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4. a) Stang, P.; Treptow, W. Synthesis 1980, 283. b) Cacchi, S.; Morera, E.; Ortar, G. Tetrahedron Lett. 1984, 4821.
5. Enone (6) was prepared via selective hydroboration/Jones oxidation of ergosterol benzoate (35%): mp 174-75 °C. We thank Mr. Tim Gallagher and Dr. Jerry Adams, SK&F Philadelphia, for providing us with a sample of enone (5). Preparation of (5) will be described by these authors elsewhere.

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