occur in radicals that have escaped their geminate original partners.

Otherwise free alkyl radicals **11** can collapse with **10** in a nongeminate recombination[11] or cyclize to cyclopentylmethyl radicals **12**. Collapsing of **12** with **10** gives adduct **4**. The ratio of products **3** and **4**, originated by nongeminate recombination is governed by the following equation: $d[3]/d[4] = k_{NG}[10]/k_{cy}$ where k_{NG} is the rate constant for collapsing of **11** with **10**. k_{NG} has been estimated to be $\sim 10^8$ M^{-1} s^{-1} for coupling between ketyls and 5-hexenyl radicals,[13] and a close value can be reasonably assumed for the more stable nitro radical anion **10**.[14] On this basis a steady-state concentration of **10** $< 10^{-3}$ M is sufficient to allow most radicals that escape the geminate recombination to cyclize before recombining with **10**.

Registry No. 1, 4900-66-7; 2, 30043-41-5; *cis*-5, 83693-44-1; *trans*-5, 83693-45-2; *cis*-6, 83693-46-3; *trans*-6, 83693-47-4; 7, 83693-48-5; 8, 83693-49-6.

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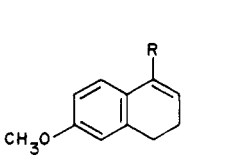
A Synthesis of (±)-Estrone Methyl Ether via the Tandem Cope–Claisen Rearrangement

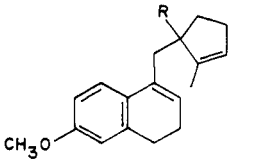
Summary: A synthesis of (±)-estrone methyl ether (**7b**) is described that employs a new approach to the construction of the estrogen skeleton invoking the tandem Cope–Claisen rearrangement.

Sir: Estrogens continue to attract attention as synthetic targets because their well-defined structures provide an opportunity to test new reactions and explore their stereochemistry. We have defined and explored the utility of the tandem Cope–Claisen rearrangement[1] and have applied it to a novel synthesis of (±)-estrone methyl ether (**7b**).[2,3]

Bromide **1b** (mp 57.5–58 °C) was prepared[4] in 68% overall yield by sequential reduction ($LiAlH_4$, Et_2O, 0 °C), mesylation (CH_3SO_2Cl, Et_3N, CH_2Cl_2, 0 °C), and displacement (LiBr, acetone, reflux) of aldehyde **1a**.[2] The anion of methyl 2-methyl-2-cyclopentene-1-carboxylate[5] (LDA, THF, −70 °C) was alkylated with bromide **1b** to afford ester **2a** in 94% yield.[6] Subsequent reduction of the ester ($LiAlH_4$, Et_2O, 0 °C) gave rise to alcohol **2b** (93% yield), which was vinylated ($Hg(OAc)_2$, CH_2=CHOEt, reflux) to provide vinyl ether **2c** (94% yield).

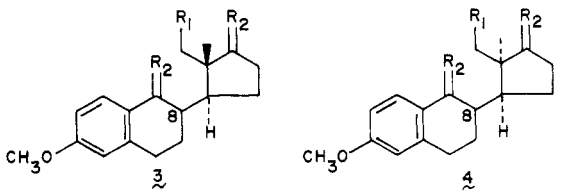


1a, R = CHO
b, R = CH_2Br



2a, R = CO_2CH_3
b, R = CH_2OH
c, R = CH_2OCH=CH_2

Thermolysis of vinyl ether **2c** (370 °C, 20 s, evacuated ampule) afforded a 2/1 mixture (60% yield) of diastereomeric aldehydes. The major component, isolated in 35% yield, was shown by single-crystal X-ray analysis to be aldehyde **3a**.[7] The structure of the minor isomer was proved to be aldehyde **4a** by the following method. Sequential exposure of aldehyde **3a** to $LiAlH_4$, Ac_2O/pyr, and



3

4

a, R_1 = CHO, R_2 = CH_2, C_8-αH
b, R_1 = CHO, R_2 = O, C_8-αH
c, R_1 = CHO, R_2 = O, C_8-βH

(1) (a) Ziegler, F. E.; Piwinski, J. J. *J. Am. Chem. Soc.* **1979**, *101*, 1611. (b) *Ibid.* **1980**, *102*, 880. (c) *Ibid.* **1980**, *102*, 6576. (d) Raucher, S.; Burks, J. E., Jr.; Hwang, K.-J.; Svedberg, D. P. *Ibid.* **1981**, *103*, 1853.
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(4) All new compounds gave correct combustion analyses or mass spectral data.
(5) Prepared in 37% yield by dripping (N_2) an 80/20 mixture of (*E*)- and (*Z*)-methyl 3-cyclopropyl-2-butenoate (Jorgensen, M.; Leung, T. *J. Am. Chem. Soc.* **1968**, *90*, 3769) through a heated (600 °C) quartz column packed with Pyrex beads.

(6) **2a**: ^1H NMR ($CDCl_3$, 270 MHz) δ 5.67 (1 H, t, J = 4.5 Hz, vinyl H), 5.47 (1 H, m, vinyl H), 3.78 (3 H, s, OCH_3), 3.58 (3 H, s, CO_2CH_3), 1.77 (3 H, m, vinyl CH_3); UV (EtOH) λ_{max} 271 nm (18 600); IR (neat) 1727 cm^{-1}; MS, m/e 312 (M^+). **2b**: IR (neat) 3400 (br d) cm^{-1}; UV (EtOH) λ_{max} 272 nm (10 500), MS, m/e 284 (M^+). **2c**: NMR ($CDCl_3$, 500 MHz) δ 6.49 (1 H, dd, J = 14.4, 6.8 Hz), 5.71 (1 H, t, J = 4.5 Hz), 5.38 (1 H, m), 4.15–3.85 (2 H, m), 3.77 (3 H, s, OCH_3), 1.64 (3 H, m, CH_3). **3a**: mp 116–117 °C (Et_2O); ^1H NMR ($CDCl_3$, 270 MHz) δ 9.64 (1 H, dd, J = 3.7, 2.2 Hz, CHO), 5.20–4.80 (4 H, m, =CH_2), 3.79 (3 H, s, OCH_3), 1.14 (3 H, s, C_{18}-CH_3); IR (neat) 2735, 1720 cm^{-1}; UV (EtOH) λ_{max} 260 nm (18 200), 296 (sh, 3000); MS, m/e 310 (M^+). **3b**: ^1H NMR ($CDCl_3$, 270 MHz) δ 9.68 (1 H, d, J = 1.2 Hz, CHO), 3.85 (3 H, s, OCH_3), 1.05 (3 H, s, C_{18}-CH_3); IR (neat) 2735, 1740, 1720, 1670 cm^{-1}; MS, m/e 314 (M^+). **3c**: mp 106–108 °C (Et_2O); ^1H NMR ($CDCl_3$, 500 MHz) δ 9.35 (1 H, s, CHO),[13] 3.84 (3 H, s, OCH_3), 2.81 and 2.74 (2 × 1 H, d, J = 18.2 Hz, CH_2CHO), 1.06 (3 H, s, C_{18}-CH_3); IR (neat film) 2735, 1740 (cyclopentanone), 1720 (CHO), 1670 (arom C=O) cm^{-1}; MS, m/e 314 (M^+). **4a**: ^1H NMR ($CDCl_3$, 270 MHz) δ 9.75 (1 H, t, J = 3.3 Hz, CHO), 5.20–4.80 (4 H, m, =CH_2), 3.79 (3 H, s, OCH_3), 1.40 (3 H, s, C_{18}-CH_3); UV (EtOH) λ_{max} 261 nm (14 000); IR (neat) 2730, 1720 cm^{-1}; MS, m/e 310 (M^+). **5a**: mp 89.5–90 °C (CH_2Cl_2–pentane); ^1H NMR ($CDCl_3$, 270 MHz) δ 9.79 (1 H, t, J = 2.9 Hz, CHO), 5.00–4.70 (2 H, m, =CH_2), 3.80 (3 H, s, OCH_3), 2.00 (3 H, s, vinylic CH_3), 1.12 (3 H, s, C_{18}-CH_3); UV (EtOH) λ_{max} 276 nm (17 700). **5b**: ^1H NMR ($CDCl_3$, 90 MHz) δ 4.95–4.65 (2 H, m, =CH_2), 3.79 (3 H, s, OCH_3), 2.05 (3 H, s, OAc), 2.03 (3 H, s, vinylic CH_3), 1.01 (3 H, s, C_{18}-CH_3); MS, m/e 354 (M^+). **5c**: ^1H NMR ($CDCl_3$, 270 MHz) δ 9.74 (1 H, t, J = 2.9 Hz, CHO), 5.00–4.70 (2 H, m, =CH_2), 3.81 (3 H, s, OCH_3), 2.05 (3 H, s, vinylic CH_3), 1.29 (3 H, s, C_{18}-CH_3); UV (EtOH) λ_{max} 274 nm (12 000). **5d**: ^1H NMR ($CDCl_3$, 90 MHz) δ 4.95–4.65 (2 H, m, =CH_2), 3.80 (3 H, s, OCH_3), 2.05 (3 H, s, OAc), 2.00 (3 H, s, vinylic CH_3), 1.12 (3 H, s, C_{18}-CH_3); MS, m/e 354 (M^+). **6a**: mp 70.5–71.5 °C; IR (neat film) 1712 cm^{-1}; UV (EtOH) λ_{max} 274 nm (15 000); MS, m/e 312 (M^+); NMR ($CDCl_3$, 270 MHz) δ 3.80 (3 H, s, OCH_3), 3.75 (3 H, s, CO_2CH_3), 2.09 (3 H, m, C_{10}-CH_3), 1.98 (3 H, m). **7a**: mp 151–152 °C (CH_3OH, lit.[3a] mp 150–152 °C), ^1H NMR ($CDCl_3$, 270 MHz) δ 6.14 (1 H, m, C_{11}-H), 3.79 (3 H, s, OCH_3), 0.94 (3 H, s, C_{18}-CH_3); IR (CCl_4) 1740 cm^{-1}; UV (EtOH) λ_{max} 262 nm (17 300), 297 (sh, 3000); MS, m/e 282 (M^+). 8-iso-**7a**: mp 152–153.5 °C (lit.[3c] mp 149.5–150 °C, CH_3OH); ^1H NMR ($CDCl_3$, 90 MHz) δ 6.01 (1 H, m, C_{11}-H), 3.79 (3 H, s, OCH_3), 0.97 (3 H, s, C_{18}-CH_3); IR (CCl_4) 1735 cm^{-1}; UV (EtOH) λ_{max} 260 nm (17 000); MS, m/e 282 (M^+).[3c] **7b**: mp 142.5–144 °C, CH_3OH (lit.[3a] mp 142–144 °C).
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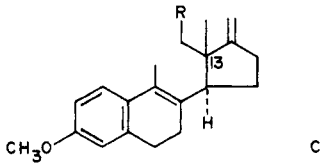
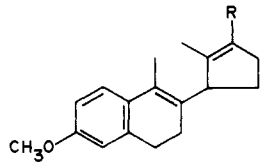
0022-3263/82/1947-5229$01.25/0

F_3CCO_2H afforded acetate **5b**, which was different from the acetate **5d** prepared in the same fashion from aldehyde **4a**. The stereochemistries of aldehydes **3a** and **4a** require the diastereomeric centers to arise during the Claisen rearrangement, preferentially having the acetaldehyde group trans to the bicyclic substituent appended to the five-membered ring. The C_8-αH stereochemistry in aldehyde **4a** was assigned by analogy. Previous studies on the tandem Cope–Claisen rearrangement have demonstrated that the lower energy Cope transition-state product is trapped by the Claisen rearrangement.[1c] Thus, **4a** would be expected to have formed by the Cope chairlike transition state followed by a Claisen rearrangement providing the cis substituents.

Occasionally, aldehydes **5a** and **5c** were obtained as minor byproducts in the tandem rearrangement. These



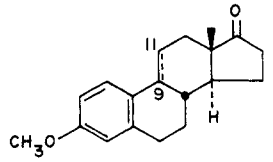
5 a, R = CHO, C_{13}-βCH_3
b, R = CH_2OAc, C_{13}-βCH_3
c, R = CHO, C_{13}-αCH_3
d, R = CH_2OAc, C_{13}-αCH_3



6 a, R = CO_2CH_3
b, R = $CH_2OCH{=}CH_2$

aldehydes could be generated as the sole products of stepwise rearrangements. Thus, thermolysis of ester **2a** (363 °C, 40 s, evacuated ampule) yielded ester **6a** in 78% yield, arising from Cope rearrangement and double bond isomerization. The initial Cope rearrangement product could never be detected, in spite of attempts to eliminate suspected fortuitous acid. Transformation of ester **6a** to vinyl ether **6b**, accomplished as described previously, followed by Claisen rearrangement (365 °C, 10 s, or 220 °C, 18 min; evacuated ampule) afforded a mixture of aldehydes **5a**/**5c** (95/5) in 95% yield, whose structures were confirmed by conversion to acetates **5b** and **5d**, respectively.

Ozonolysis of aldehyde **3a** (O_3, CH_2Cl_2, −50 °C; DMS) provided tricarbonyl compound **3b** in 70% yield. Epimerization of **3b** ($NaOCH_3$/$HOCH_3$, 25 °C) gave rise to a mixture of diketo aldehydes **3b**/**3c** (1/4), free from aldol products, from which **3c** could be isolated (69% yield). Subjection of tricarbonyl **3c** to a modified McMurry reaction[8] ($TiCl_3$, Zn/Ag, DME, no dilution, reflux) provided (±)-9,11-dehydroestrone methyl ether (**7a**) in 56% yield,



7 a, 9,11-dehydro
b, 9,11-dihydro

whose spectroscopic data was in accord with literature values.[3a] Formation of the more strained 8-iso-9,11-dehydroestrone methyl ether (from **3b**) occurred in only 15% yield. The selectivity of the olefin-forming reaction is viewed as proceeding by initial ketyl formation at the aromatic ketone, which would be expected to have the lowest reduction potential of the three carbonyl groups.

Finally, ketone **7a** was converted (K/NH_3; CrO_3)[9] to (±)-estrone methyl ether (**7b**) whose spectroscopic properties (except optical rotation) were identical with those of a sample of (+)-estrone methyl ether.[10] Estrone methyl ether has been converted to estrone.[11]

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(13) The lack of visible vicinal coupling between the sp^2 aldehyde proton and the adjacent methylene protons requires comment. Powles and Strange[12] have derived the equation $J(180-\phi) = 2.54 + a_1 \cos(180-\phi) + a_2 \cos 2(180-\phi) + 0.69 \cos 3(180-\phi)$ for the vicinal coupling constant as a function of dihedral angle $(180-\phi)$. With use of $a_1 + a_2 = 5.7$ as a mean value and $J(180°) = 8.3$ Hz and $J(60°) = 0.1$ Hz as determined by Alexander and Pople[14] for acetaldehyde, the value of $a_1 = 2.3$ provides all positive coupling constants with $J(180°) = 8.9$ Hz and $J(60°) = 0.4$ Hz (reported,[12] 0.5 Hz). The average conformation has the sp^2 H bisecting the methylene protons within approximately 10° ($J(70°) = 0.1$ Hz, $J(50°) = 0.6$ Hz). These numbers are at the resolution threshold of the 500-MHz NMR spectrometer (5600 Hz/16K data points = 0.35 Hz/dp). All such coupling constants for aldehydes reported herein are in close agreement with this curve.
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Stereochemistry of Trifluoroacetolysis and Brominolysis of the Cyclohexyl–Tin Bond

Summary: (*cis*- and *trans*-4-methyl- and 4-*tert*-(butylcyclohexyl)triisopropylstannanes have been synthesized and fully characterized. Trifluoroacetolysis of these compounds proceeds stereospecifically with retention of configuration at carbon. Electrophilic bromination is characterized by a fine energetic balance between inversion and retention pathways, with the former favored for the equatorial carbon–tin bonds and the latter for axial carbon–tin bonds in these triisopropylstannanes. Bromination under free-radical conditions yields a statistical mixture of the *cis*- and *trans*-4-alkylcyclohexyl bromides, a result appropriate for bromine atom transfer to a 4-alkylcyclohexyl free radical.

Sir: The demonstration by Jensen and Davis,[1] and subsequently others,[2,3] that electrophilic bromodestannylation could have a preferred inversion pathway (e.g., I) has added a new dimension to our concepts of aliphatic electrophilic subsitution (S_E2), particularly when it is recalled that retention of configuration uniformly characterizes the favored pathway for bromo- and protiodemercuration of alkylmercurials (e.g., II and III).[4] In this latter context,

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