(11) For S_N2-type processes β-hydrogen isotope effects CH_3/CD_3 of the order of 1.1–1.2 are normal, whereas for E2-type processes *primary* β-hydrogen effects of the order of 2–6 are to be expected. (a) Harris, J. M. *Prog. Phys. Org. Chem.* **1974,** *11,* 89–110. (b) Sunko, D. E.; Szele, I.; Hehre, W. J. *J. Am. Chem. Soc.* **1977,** *99,* 5000–5005. (c) Seib, R. C.; Shiner, V. J., Jr.; Sendijarević, V.; Humski, K. *Ibid.* **1978,** *100,* 8133–8137. (d) Reference 10a. (e) Cook, D.; Hutchinson, R. E. J.; MacLeod, J. K.; Parker, A. J. *J. Org. Chem.* **1974,** *39,* 534–538.
(12) Lambert, J. B.; Mark, H. W.; Holcomb, A. G.; Magyar, E. S. *Acc. Chem. Res.* **1979,** *12,* 317–324.
(13) Drabicky, M. J.; Myhre, P. C.; Reich, C. J.; Schmittou, E. R. *J. Org. Chem.* **1976,** *41,* 1472–1473.
(14) Harrington, C. K. Ph.D. Thesis, The Ohio State University, 1976; *Diss. Abstr.* **1976,** *37,* 2248-B.
(15) Poulter, C. D.; Rilling, H. C. *Acc. Chem. Res.* **1978,** *11,* 307–313. Poulter, C. D.; Satterwhite, D. M.; Rilling, H. C. *J. Am. Chem. Soc.* **1976,** *98,* 3376–3377.
(16) (a) Gassman, P. G.; Talley, J. J. *J. Am. Chem. Soc.,* preceding paper in this issue. (b) Creary, X. *J. Org. Chem.* **1979,** *44,* 3938–3945.

K. M. Koshy, Thomas T. Tidwell*
Department of Chemistry, University of Toronto
Scarborough College, West Hill, Ontario, Canada M1C 1A4
Received August 20, 1979

Reductive Alkylation of Enediones. 1

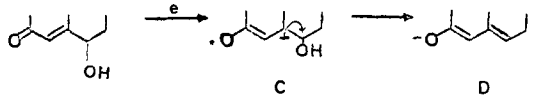
Sir:

We report here on the successful application of the reductive alkylation method[1] to enedione systems, thus allowing the transformation A → B. This transformation could be very

A B

useful for the construction of polycyclic systems such as the corticosteroids and the fusidic acids which have a carbonyl function at C_{11}.

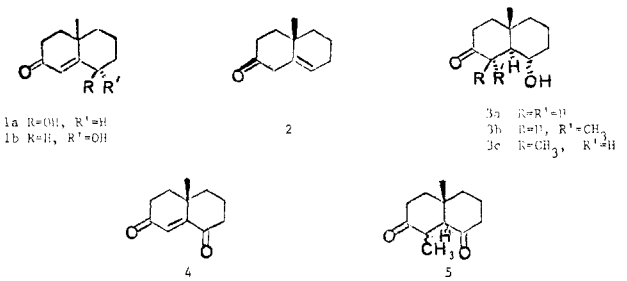
The first possibility which we envisaged involved the generation of a kinetic enolate by reduction of a γ-hydroxyenone. The process which is well known to involve loss of oxygen via the path C → D,[2] but it appeared to us likely that this loss of



C D

a hydroxyl group would be strongly conformation dependent, so that the reported results could be due to the axial nature of the hydroxyl group (better overlap for elimination).

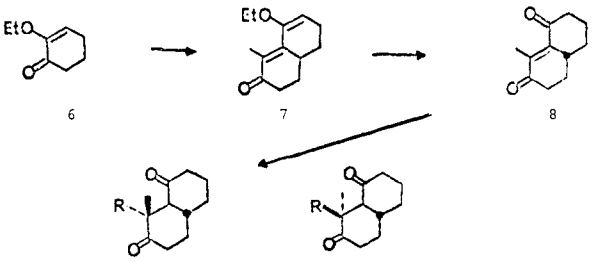
In keeping with this view, we have now found that, in contrast to 8β-hydroxy-10-methyl-$\Delta^{1,9}$-2-octalone[3] (**1a**), mp 57–58.5 °C, which with lithium in ammonia–tetrahydrofuran afforded only the β,γ enone **2** under a variety of experimental conditions, reduction of the equatorial isomer **1b**,[3] mp 121–122 °C, furnished hydroxy ketone **3a**. Quenching the reduction mixture from **1b** with methyl iodide resulted in formation of ketones **3b** and **3c**, in 66 and 15% yields, respectively.[4]



1a R=OH, R'=H
1b R=H, R'=OH
2
3a R=R'=H
3b R=D, R'=CH_3
3c R=CH_3, R'=H
4
5

Even more generally useful results were obtained from the reductive alkylation process applied to the enedione **4** (mp 70–71.5 °C, after sublimation of 70–80 °C at 0.1 mm), obtained by Jones oxidation of **1a,b.** Exposure of **4** to lithium (4 equiv) in refluxing ammonia–tetrahydrofuran (2:1), followed by quenching with methyl iodide, evaporation of ammonia, and aqueous workup, furnished three monomethylated isomers of **5,** in yields of 19, 25, and 19% after chromatographic separation on silica gel. No material derived from alkylation at the ring junction could be detected.

Extension of this sequence to bicyclic enediones unsubstituted at the ring junction could be performed in the following manner. Aprotic conjugate addition of enol ether **6** (LDA in tetrahydrofuran −78 °C) with 2-trimethylsilyl-1-penten-3-one, followed by cyclization with sodium methoxide in refluxing methanol and acid hydrolysis, furnished 1-methyl-$\Delta^{1,9}$-octalin-2,8-dione (**8**) in ~50% yield.

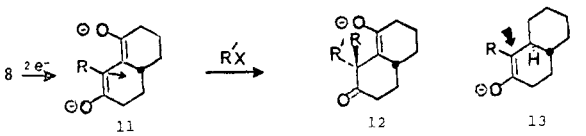


6 7 8

9a R= CD_3 9c R= CH_2Ph 10a R= CD_3
9b R= $CH_2CH=CH_2$ 9d R= 3,5-dimethyl-4-isoxazolylmethyl 10b R= $CH_2CH=CH_2$

Treatment of **8** with lithium in refluxing ammonia–tetrahydrofuran, followed by quenching with trideuteriomethyl iodide, gave, after chromatography on silica gel, a 66% yield of a mixture of the equatorially alkylated isomer **9a** and the axially alkylated isomer **10a,** in a ratio of 85:15.[5] The use of allyl bromide as alkylating agent permitted isolation of dione **9b** and dione **10b,** mp 76–77 °C, in yields of 48 and 15%, respectively, after chromatography on silica gel. The pronounced stereoselectivity of alkylation in this system, which results in the introduction of an equatorial substituent, was increased by the use of sterically more hindered alkylating agents: alkylation of **8** using benzyl bromide furnished a single dione **9c** (mp 106–107 °C after chromatography on silica gel; methyl at δ 1.40 in NMR). None of the axially alkylated dione could be detected. The use of 4-bromomethyl-3,5-dimethylisoxazole resulted in the formation of dione **9d** (mp 137 °C; methyl at δ 1.34) in 67% yield, after chromatography on silica gel.[6]

The remarkable preference of dienediolates for undergoing alkylations leading to equatorial products (**11** → **12**) is in contrast to the well-established[7] axial mode of alkylation of enolates such as **13** obtained via the reduction of the usual octalone system.



11 12 13

We suggest that this stereochemical result derives from the distortion of ring labeled B in **11** toward a half-boat to avoid the eclipsing interaction of the O^- and R substituents. The resulting rotation, shown by the arrows, results in moving R toward the center of the ring, thus exposing the α face. Whatever its exact origin, the stereoselectivity and regioselectivity of the reductive alkylation of enediones of type **8,** can be used to special advantage in the synthesis of corticosteroids, as we illustrate in the following paper.

Acknowledgment. We thank the National Institutes of Health and the National Science Foundation for their support of this work.

0002-7863/80/1502-1218$01.00/0

References and Notes

(1) Stork, G.; Rosen, P.; Goldman, N.; Coombs, R. V.; Tsuji, J. *J. Am. Chem. Soc.* **1965,** *87,* 275–286.

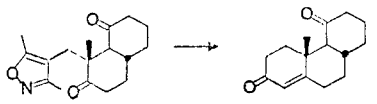
(2) Amendolla, C.; Rosenkranz, G.; Sondheimer, F. *J. Chem. Soc.* **1954,** 1226–1233. Anthousen, T.; McCabe, P. H.; McGrindle, R.; Murray, R. D. H. *Tetrahedron* **1969,** *25,* 2233–2239. Ireland, R. E.; Beslin, P.; Giger, R.; Hengartner, V.; Kirst, H. A.; Maag, H. *J. Org. Chem.* **1977,** *42,* 1267–1276. For an exception, see Barton, D. H. R.; Laws, G. F., *J. Chem. Soc.* **1954,** 52.

(3) Compounds **1a** and **1b** were obtained via epoxidation of the conjugated dienol ether from 10-methyl-$\Delta^{1,4}$-2-octalone; cf. Wege, P. M.; Clark, R. D.; Heathcock, C. H. *J. Org. Chem.* **1976,** *41,* 3144–3148, note 26.

(4) Assignment of stereochemistry is based on the known stereochemistry of alkylation of systems of this type; cf. Matthews, R. S.; Girgenti, S. J.; Folkers, E. A. *J. Chem. Soc., Chem. Commun.* **1970,** 708. The major (isomer **3b** had its methyl absorptions at δ 0.95 (s) and 1.32 (J = 8 Hz). The epimer **3c** had δ 1.12 (s) and 1.19 (J = 8 Hz). That **3b** is the kinetic isomer was shown by base equilibration to a 60:40 mixture of **3b** and **3c.**

(5) Assignment of stereochemistry was made on the assumption that the equatorial methyl would be the more shielded (higher field) by the carbonyl at "C_{11}". The chemical shift of the (axial) methyl group in **9a** was 1.33 ppm; the (equatorial) isomer **10a** had a shift of 1.22 ppm. The same shifts were observed for the isomers **9b** and **10b.** The ring fusion of diones **9a–d** results from kinetic protonation and is initially trans. Base-catalyzed isomerization leads to a 60:40 trans–cis mixture in each case. The stereochemistry assigned **9a–d** was confirmed, in any event, by the construction of known steroids (see accompanying communication): Stork, G.; Logusch, E. W. *J. Am. Chem. Soc.*, following paper in this issue.

(6) Dione **9d** could be converted into the tricyclic dione **14** (mp 101–103 °C)



9d 14

via the usual sequence of hydrogenation over W-2 Raney nickel, followed by base-catalyzed cyclization (see ref 7).

(7) Stork, G.; Danishefsky, S.; Ohashi, M. *J. Am. Chem. Soc.* **1967,** *89,* 5459–5460. Stork, G.; McMurry, J. E. *Ibid.* **1967,** *89,* 5464–5465.

Gilbert Stork,* E. W. Logusch

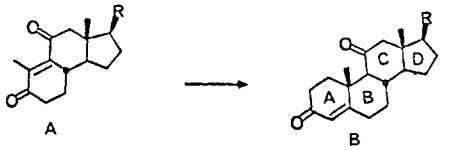
Department of Chemistry, Columbia University
New York, New York 10027

Received September 4, 1979

Reductive Alkylation of Enediones. 2. Synthesis of Corticosteroids

Sir:

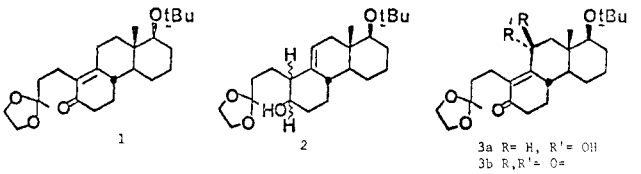
With the spectacular exception of Johnson's polyene cyclization route to cortisone,[1] the construction of corticosteroids usually involves the introduction of the 11-oxygen function at a very late stage of their synthesis.[2] A particularly expeditious route within the classical DC → B → A approach would result, however, if it were possible to achieve the transformation A → B in two or three steps. The work on the reductive alkylation



A B

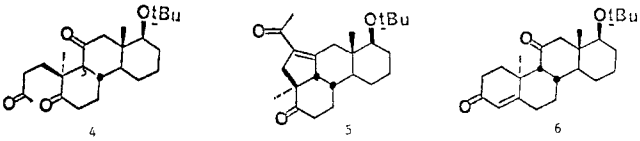
of enediones described in the accompanying communication[3] suggested that this might be possible. We now describe experiments which eventually led to a very simple construction of adrenosterone (B, R = carbonyl oxygen).

The previously reported tricyclic enone **1,** which is conveniently prepared by annulation using the silylated enone methodology,[4] was converted into the homoallylic alcohol **2** by sodium borohydride reduction in refluxing methanol of the corresponding dienol acetate (prepared by refluxing **1** with potassium *tert*-butoxide in benzene, followed by quenching with acetic anhydride). Epoxidation of **2** with *m*-chloroperbenzoic acid, followed by Collins oxidation and exposure to methanolic sodium hydroxide, furnished the hydroxyenone **3a** (mp 88–91 °C) in 78% yield from **1.** Oxidation of **3a** with pyridinium chlorochromate furnished enedione **3b** (mp 109–111 °C) in 89% yield.



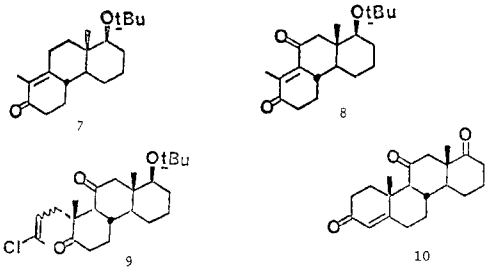
1 2 3a R= H, R'= OH 3b R,R'= O=

Treatment of **3b** with lithium in ammonia–tetrahydrofuran (2:1), followed by quenching with methyl iodide and hydrolysis with aqueous acetic acid, provided triketone **4** in ~70% yield. The equatorial configuration of the newly introduced methyl group at C-10 was strongly suggested by its chemical shift of 1.20 ppm. This inference was confirmed when cyclization of **4** in refluxing methanolic sodium hydroxide afforded enone **5** (mp 101–102 °C) and enone **6** (mp 119–121 °C) in a ratio of 3:1. The latter result is understandable, since cyclization to the 9β,10α-*D*-homoandrostane skeleton of **6** requires ring B to assume a twist-boat conformation.



4 5 6

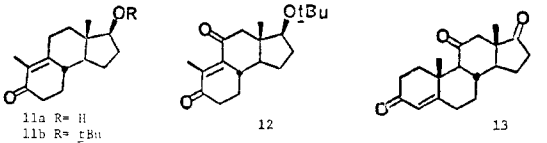
The stereochemical outcome of the reductive alkylation of the enedione **1,** which essentially parallels results in the simple bicyclic model series, thus required that the carbon atoms needed for ring A, rather than the methyl group, be introduced last. This was accomplished in the following manner. The tricyclic enone **7** (mp 91–91.5 °C) was prepared in 78% yield from 5-*tert*-butoxy-10-methyl-$\Delta^{1,9}$-2-octalone, in a manner similar to that described for enone **1.** Enone **7** was converted into dione **8,** mp 148.5–150.5 °C, in 74% yield, using the method described for **3.**



7 8 9 10

Reductive alkylation of **8** by aprotic Michael addition using silyl enones was unfortunately unsuccessful, possibly because of facile electron transfer from the intermediate dienediolate. Other annulating agents could, however, be used successfully: the modified Wichterle reagent,[5] 4-bromo-2-chloro-2-butene, thus afforded dione **9.** The latter was converted in 37% yield from **3** into (±)-*D*-homoadrenosterone (**10**), mp 199–201 °C,[6] via a sequence which involved refluxing formic–perchloric acid,[7] hydrolysis of the intermediate C-17a formate, and Jones oxidation.

The above sequence was applied with equal success to the series of compounds possessing a five-membered D ring, starting with the optically active enone **11a.**[8] The corresponding *tert*-butyl ether **11b,** mp 77.5–78.5 °C was converted in the usual manner in 71% overall yield into the enedione **12**



11a R= H 11b R= tBu 12 13

[mp 131–132.5 °C, $[\alpha]^{25}_D$ 29° (c 1.0, methanol)]. The latter on reductive alkylation with the Wichterle reagent and cycli-

0002-7863/80/1502-1219$01.00/0