

REGIOSELECTIVE FUNCTIONALIZATION OF *cis*-BICYCLO[3.3.0]OCTENONE DERIVATIVES. OXYMERCURATION/REDUCTION
versus HYDROBORATION/OXIDATION. ACETAL GROUPS AS REGIO- AND STEREOSELECTIVE CONTROL ELEMENTS

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Cyclic acetal groups at the position 8 of the *cis*-bicyclo[3.3.0]octane system may act as regio- and stereoselective control elements, respectively, in hydroboration and oxymercuration reactions. Whereas the regioselectivity observed in hydroborations must be ascribed to homoallylic inductive effects, and leads predominantly to *exo*, 1,3-bifunctional relationships, the effect of acetal group in oxymercuration is mainly stereoselective due to coordination of mercury acetate with the nonbonding electron pairs of the *endo*-oxygen atom of the acetal group, and leads predominantly to *exo*, 1,4-bifunctional relationships.

Owing to the *cis*-ring junction, the attack of reagents to the *cis*-bicyclo[3.3.0]octane system is highly stereoselective, occurring almost invariably on the convex face of the molecule.¹⁾ The concurrent problem of the regioselective functionalization of positions 2 or 3 of this system has been much less satisfactorily solved. Thus, whereas *exo-cis*-bicyclo[3.3.0]octan-2-ol (**2a**) can be selectively obtained by reduction of the corresponding *exo*-epoxide, hydroboration of *cis*-bicyclo[3.3.0]oct-2-ene (**1**) gives nearly a 1:1 mixture of 2-*exo* (**2a**) and 3-*exo* (**2b**) alcohols.^{1b)}

In connection with a research project concerning the regioselective 1,4-bifunctionalization of polyquinanes²⁾ we have studied the hydroboration of *cis*-bicyclo[3.3.0]oct-7-ene-3-one³⁾ and *cis*-bicyclo[3.3.0]oct-7-ene-2-one,⁴⁾ with the corresponding carbonyl groups conveniently protected as cyclic acetals **3** and **5** in order:

- i) to prevent them from reduction by the hydroborating agent,
- ii) to assess the possibility that steric and/or electronic effects of the acetal group may induce some regioselectivity in hydroboration reactions, compared to that previously observed in the case of **1**, and
- iii) to study the effects of different substituents, in the hydroborating agents, on the regioselectivity of the reaction.

As anticipated, hydroboration of acetal **3** with different boranes (Table 1) did not exhibit any kind of regioselectivity, and a 1:1 mixture of two isomeric alcohols **4a** and **4b** was always obtained. However, hydroboration of acetal **5** under kinetic conditions with $\text{BH}_3\cdot\text{THF}$ and $\text{BH}_3\cdot\text{SMe}_2$ gave 70-77% yield of two regioisomeric alcohols, A and B, in a 68:32 ratio. In contrast to acetal **3**, some regioselectivity was now observed, and further studies were pursued with boranes bearing alkyl substituents of increasing size in order to get some insight in the factors governing the observed regioselectivity.

As shown in Table 1, a similar A:B ratio was observed with *tert*-butylborane, and a small increase in the amount of alcohol A, in front of B, if 9-BBN was the hydroborating agent. However, a signi-

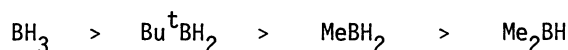
ficant improvement in regioselectivity, favoring alcohol A over B (85:15), was observed using disiamylborane, a fact that induced us to conclude that isomer A should be the *exo*, 1,4-disubstituted derivative ξ_b . Careful spectroscopic analysis by ^{13}C and proton NMR showed, however, that the predominant regioisomer A is, in fact, the *exo*, 1,3-disubstituted product ξ_a .⁵⁾

Although coordination of the nonbonding electron pairs of the acetal oxygen atom with the electron-deficient hydroborating species could, in principle, explain the observed regioselectivity, the stereochemistry (*exo* rather than *endo*) points out that other effects must be operating, as it is clear by inspection of the molecular models.

In fact, hydroboration of *endo-p*-nitrobenzoate derivative ζ with $\text{BH}_3\cdot\text{SMe}_2$ gave, after hydrolysis, a 80:20 mixture of ξ_a and ξ_b , in 91% yield. Here, the hydroborating agent reacts with a substrate having a more electron-deficient oxygen atom, owing to the presence of the *p*-nitro group, and yet the regioselectivity is greater than the one observed in the case of acetal ξ (see entry 2 of Table 1).

The effect of the acetal group is, therefore, electronic rather than one of steric nature and the observed regioselectivity must be ascribed to inductive effects as those observed in hydroboration of allylic and homoallylic derivatives bearing electron-withdrawing substituents.⁶⁾

On the other hand, MNDO calculations show that the energy of the LUMO of substituted boranes⁷⁾ decreases in the order



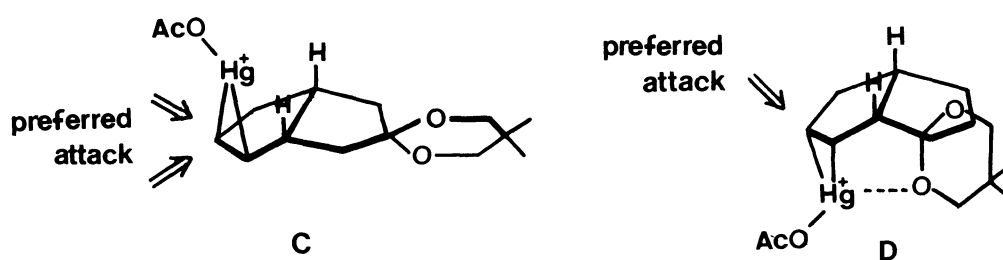
and one could expect that the more substituted boranes, which are the more electrophilic ones, would be more sensitive to inductive and/or field effects and show greater regioselectivity, as it is actually observed.

A series of hydroborations of acetal ξ with boranes bearing either electron-withdrawing (haloboranes) or π -electron donating substituents (alkoxyboranes) was performed in order to see how the electrophilic character of the borane would affect the A:B ratio of the regioisomeric alcohols. But, surprisingly enough, none of these alcohols was detected in the hydroboration of both, chlorothylborane and catecholborane, a new compound being isolated as the exclusive reaction product, which was identified as ether η resulting from reduction of the acetal group.⁸⁾

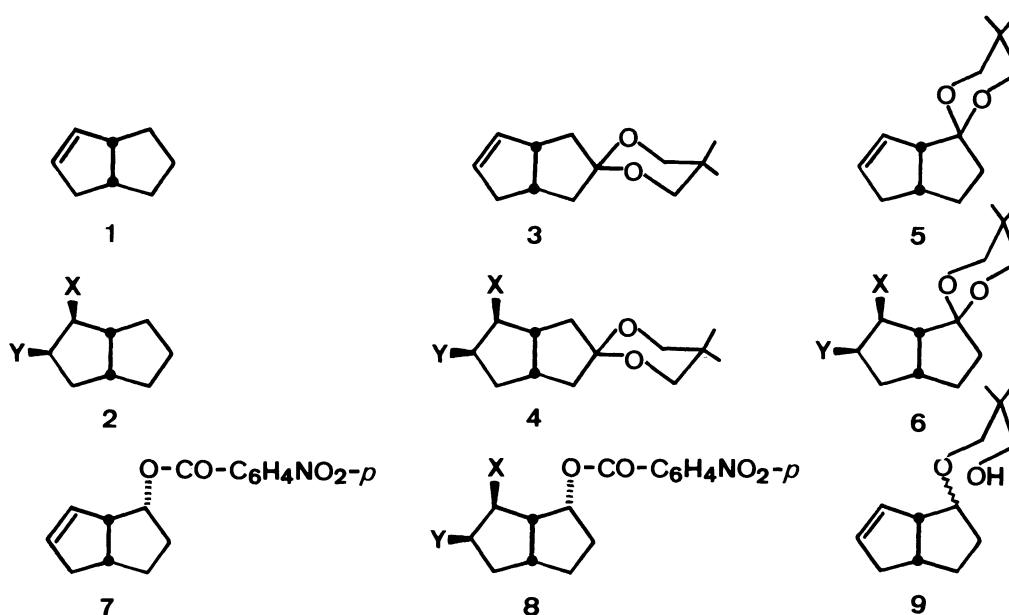
In any case, since the observed regioselectivity was in favor of a 1,3-bifunctional relationship, rather than the desired 1,4, we decided to study the oxymercuration/ NaBH_4 reduction method, which is the alternative Markownikoff method to the anti-Markownikoff hydroboration/oxidation sequence for "hydration" of olefins.

Whereas oxymercuration of acetal ξ with $\text{Hg}(\text{OAc})_2/\text{THF}/\text{H}_2\text{O}$ was completely stereoselective and gave, in 80% yield, a 7:3 mixture of two *exo*-regioisomers ξ_b : ξ_a , the oxymercuration of acetal ζ was more regioselective but less stereoselective, affording a 9:1 mixture of 3,7- and 3,8-derivatives, η_b : η_a , in which the predominant regioisomer was, however, a 7:3 mixture of *exo*:*endo*.

As stated at the very beginning of this communication, the attack of $\text{Hg}(\text{OAc})_2$ to the *cis*-bicyclo[3.3.0]octane system of acetal ζ must occur on the convex face (*exo*) of the molecule (see C) and competitive *cis* and *trans* additions would explain the formation of *exo* and *endo* isomers. However, the complete stereoselective formation of *exo*-alcohols from ξ should be explained either by an exclusive, but not very probable, *cis*-addition or by a more probable *trans*-addition to an *endo*-organomercury intermediate (D) stabilized by coordination with the nonbonding electron pairs of the acetal oxygen atoms, as observed in oxymercuration of related monocyclic substrates.⁹⁾



Regarding to the regioselectivity, the observed 9:1 and 7:3 ratios of $\underline{4}b:\underline{4}a$ and $\underline{6}b:\underline{6}a$, respectively, must be ascribed to steric effects since the more favored attack, either *endo* or *exo*, will occur at the less hindered 7 position.



a, X=OH, Y=H ; b, X=H, Y=OH

TABLE 1. COMPOSITION OF REACTION MIXTURES FROM HYDROBORATION AND OXYMERCURATION

Reagent	Ref.	$\underline{4}a:\underline{4}b$ ratio ^{a, b)}	A:B = $\underline{6}a:\underline{6}b$ ratio ^{a, c)}	$\underline{8}a:\underline{8}b$ ratio	$\underline{9}$
BH ₃ .THF	10	50:50	62:38	-	-
BH ₃ .SMe ₂	11	-	61:39	80:20	-
TxBH ₂	12	50:50	62:38	-	-
9-BBN	13	50:50	64:36	-	-
(Sia) ₂ BH	14	50:50	85:15	-	-
TxBClH	15	-	-	-	65%
Catechol-borane	8	-	-	-	97%
Hg(OAc) ₂	16	10:90 ^{d)}	30:70	-	-

a) Chemical yields 70-90%. b) Composition determined by NMR of purified mixture (column chromatography). c) Composition determined by gas chromatography and preparative column chromatography. d) predominant regioisomer is a 7:3 mixture of *exo:endo*.

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