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Introduction

The addition of electron-deficient boranes to alkenes is one of the most common reactions to produce organoboranes.^{1,2} The resulting alkylboranes are easy-to-handle and highly versatile intermediates that participate in many synthetically useful transformations. Perhaps the most common reaction of organoboranes is their oxidation by hydrogen peroxide in an alkaline medium to furnish the corresponding alcohols regio- and stereospecifically.³ The hydroboration (HB) of alkenes is

a traditional and well-known organic transformation where the governing stereochemical principle is the addition of hydrogen and BH_2 to the same π -face (*syn*-addition). This reaction, in principle, proceeds *via* a four-membered transition state (Scheme 1).^{1,2} Most olefins readily undergo HB under the latter conditions, usually giving the corresponding anti-Markovnikov product, and the subsequent oxidation step with hydrogen peroxide proceeds with retention of configuration.

These observations lead to the generalization that HB takes place *via* an anti-Markovnikov *syn*-addition from the less hindered side of the double bond. Even the HB of terminal alkynes occurs in an anti-Markovnikov stereospecific fashion, where the *syn* addition also results from HB on the same side of the alkyne.

After a plethora of literature reports on olefin HB reactions, the following question arises: is it possible to obtain a *trans*-hydroboration product? The answer is yes, but it has never been reported under traditional HB conditions. To the best of our knowledge, no examples of olefin *trans*-HB have been described in the literature. Herein, we report a *trans*-hydroboration-

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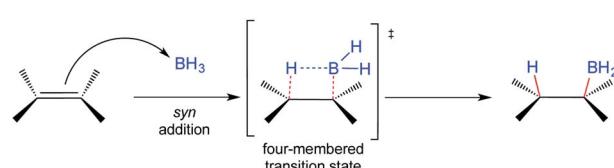
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† Electronic supplementary information (ESI) available: Detailed experimental procedures, characterization of all the isolated compounds, computational details, and the Cartesian coordinates of all the stationary points. CCDC 1921283–1921286. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/d0sc01701a

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Scheme 1 General mechanism for the hydroboration reaction of alkenes.



oxidation product from a hydroboration-*retro*-hydroboration pathway employing cholesterol (**1**) and diosgenin (**2**) as substrates. These outcomes violate, in principle, all HB reported mechanisms so far.

Results and discussion

The first application of the hydroboration–oxidation (HBO) procedure to the double bond in cholesterol (**1**, Fig. 1) was reported in 1959 simultaneously by Wechter⁴ and Sondheimer.^{5,6} Wechter reported that the HB reaction employing $\text{BH}_3 \cdot \text{THF}$ yielded a mixture of dialkyl boranes in 98% of isolated yield. Upon oxidation ($\text{H}_2\text{O}_2/\text{NaOH}$), the crude product was found to consist of 5α -cholestane- $3\beta,6\alpha$ -diol (**1a**, 78%), 5β -cholestane- $3\beta,6\beta$ -diol (**1c**, traces), and a third compound reported as “not characterized” (see Fig. 1). In parallel, Sondheimer reported the use of $\text{BH}_3 \cdot \text{OEt}_2$ and cholesterol to deliver, after oxidation using H_2O_2 in ethanolic KOH, a mixture of compounds consisting of **1a** (68%), **1c** (20%), and recovering some **1** (9%). In general, most of the HBO studies on Δ^5 -steroids describe the generation of only one alcohol with the stereochemistry of **1a**.⁷

We decided to perform the HBO of **1** and **2** (Fig. 1).^{8,9} The reactions were subjected to a thorough temperature study (from 20 °C to –20 °C). In our hands, for both substrates, the crude contained three main components and ultimately four products were isolated and fully characterized.

Due to the steric shielding exerted by Me-19, not surprisingly the major products (**1a** and **2a**) arose *via* hydroboration of the α -steroidal face.¹⁰ It is remarkable that the lowering of the reaction temperature led to lower yields of compounds type **a** (see Table 1).^{11–13} Compounds **1b** and **2b**¹⁴ are the Markovnikov addition products. These compounds have been recently reported employing transition-metal-catalyzed asymmetric HB reactions.^{15,16} However, under the typical HB conditions (as in our case), they were unexpectedly obtained in synthetically meaningful yields (8–18%). It is also notable that their formation is favored with the decrease of temperature. The isolation of compounds type **c** was challenging. However, after several purifications by column chromatography, both **1c** and **2c**

Table 1 Isolated yields from HBO of **1** and **2** at different temperatures

Diol type	Isolated yields at different temperatures (%)				
	20 ^a °C	10 °C	0 °C	–10 °C	–20 °C
Diols derived from cholesterol (1)					
1a	66	62	59	54	40
1b	9	10	12	14	17
1c	Traces	Traces	Traces	Traces	Traces
1e	22	24	27	30	38
Diols derived from diosgenin (2)					
2a	65	61	55	52	41
2b	8	10	12	15	18
2c	Traces	Traces	Traces	Traces	Traces
2e	21	23	26	29	36

^a Reactions carried out at rt (25 °C) provided similar yields.

successfully crystallized from an enriched fraction of **c**. The full 1D and 2D NMR characterization data are detailed in the ESI.† Compounds of type **d** were not detectable, and the unreacted starting materials were not recoverable from any of the reactions.

Unexpectedly, we also found the “*trans*”-HBO products, **1e** and **2e**,¹⁷ under classical HB conditions! The yields of these unexpected stereoisomers are 21–38%, surprisingly high when considering their nature. At room temperature, yields of products type **e** are about one-third of the HBO products type **a**. The $5\alpha,6\beta$ -stereochemistry of **1e** and **2e**¹⁸ are confirmed by NMR; for further details, see the ESI.†

For structures **b**, **c**, and **e**, the observed stereochemistry in solution is supported by the single-crystal X-ray crystallography structure determinations of compounds **2b**, **1c**, **2c**, and **1e**, respectively (see ESI and CIF files deposited with the CCDC†). Of particular interest is the “*trans*” product **1e**, in which the 6β -OH and 19-Me groups are assumed to induce steric repulsion (Fig. 2). Indeed, the $\text{O}6 \cdots \text{C}19$ separation, 3.029(4) Å, is shortened by 0.19 Å as compared to the van der Waals distance. However, since the OH group is free to rotate, there are no

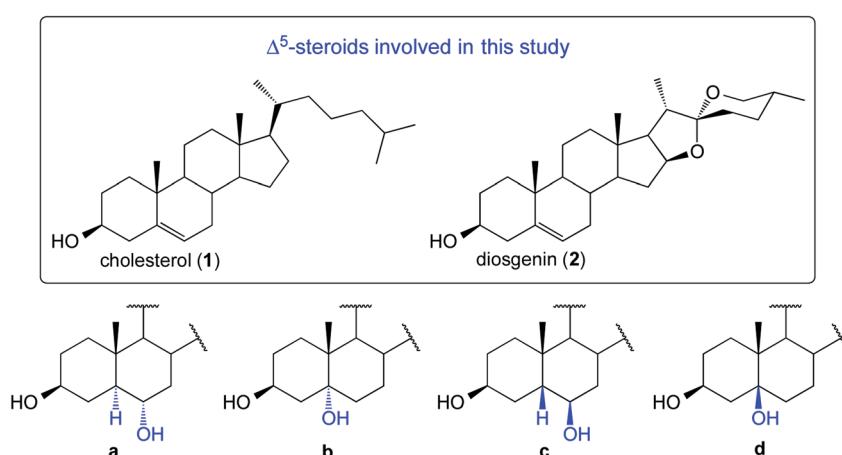


Fig. 1 Structures of four possible products derived from the HBO reaction of substrates **1** and **2** (structures type **a**–**d**).



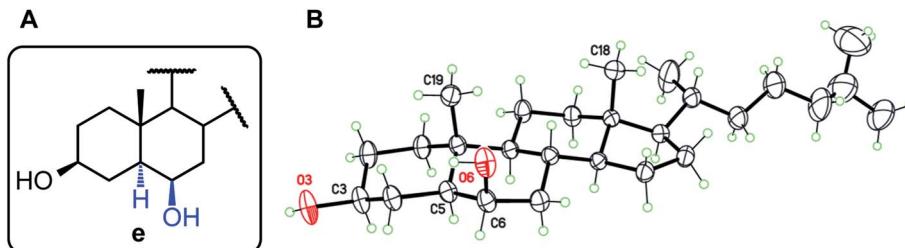


Fig. 2 (A) Structure type **e** (derived from the HBO reaction of **1** and **2**). (B) Molecular structure for compound **1e** with displacement ellipsoids at 30% probability level.

occurrences of destabilizing $H \cdots H$ contacts, and both 3β and 6β hydroxyl groups are engaged in classical intermolecular hydrogen bonds, to form supramolecular chains in the crystal. The same situation is observed for **1c** and **2c**.

To elucidate the formation of the unexpected HBO products type **e**, we performed a series of quantum chemical computations at the DLPNO-CCSD(T)^{19–21}/def2-TZVPP²² level by taking the PBE0 (ref. 23) structures from a model composed of two rings (a decalin framework, see Fig. 3), and considering the solvent effects (THF) *via* the SMD²⁴ approximation. Entropic contributions and thermal corrections were computed at the SMD-PBE0-D3 (ref. 25)/def2-TZVP level at 273.15 K. Hydroboration has been theoretically studied by several groups.^{26–28} Validation of this methodology and further details are provided in the ESI.† All these computations were done in Gaussian 16 (ref. 29) and Orca 4.1.1.³⁰ Considering that the alcohol is formed with retention of configuration in a subsequent oxidation step, we focus our analysis on the HB mechanism; thus, we label the alkylborane system as **1a'** that produces **1a** after the oxidation.

The Gibbs energy pathways for the suprafacial HB additions of **1** are illustrated in Fig. 3. The smallest barrier ($\Delta G^\ddagger = 2.7 \text{ kcal mol}^{-1}$) is obtained for one of the α -additions. It is easily explained due to the presence of Me-19. As is expected, the difference between anti-Markovnikov and Markovnikov barriers ($\Delta\Delta G^\ddagger = 3.4 \text{ kcal mol}^{-1}$) favors the former addition. Since the addition involves the bridgehead C-5, these transition states (TSs) are connected to twisted-chair conformations (**INT-1a'** and **INT-1b'**), which are more stable than the reactants by 5.4 and 4.5 kcal mol⁻¹, respectively. The barriers to obtain the final products are relatively low (2.2 and 3.2 kcal mol⁻¹) and correspond to a conformational arrangement to form the final products with a *trans*-A/B rings fusion. The formation of both **1a'** ($\Delta G_{\text{rxn}} = 13.5 \text{ kcal mol}^{-1}$) and **1b'** ($\Delta G_{\text{rxn}} = 10.4 \text{ kcal mol}^{-1}$) is exergonic in nature. At this point, there are no surprises.

The formation of **1c'** and **1d'** involves an additional conformational change to provide the *cis*-A/B rings fusion. The barriers for HB additions at the β -face are similar to that computed for **1b'** ($\sim 6 \text{ kcal mol}^{-1}$). The first conformational

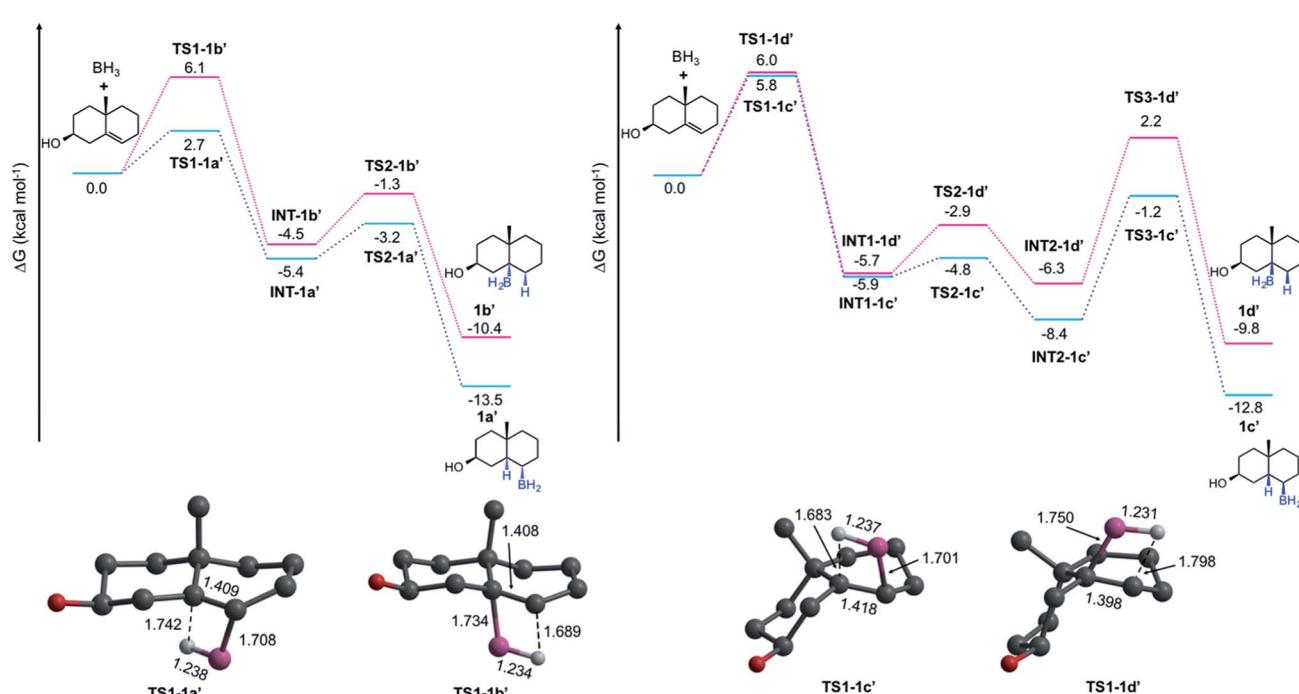


Fig. 3 Gibbs energy profiles (in kcal mol^{-1}) of hydroboration of the decalin model of **1** and transition state structures for the first steps. Bond distances are in Å. In the depicted structures, H atoms are omitted for clarity, except the H atom involved in the hydroboration.



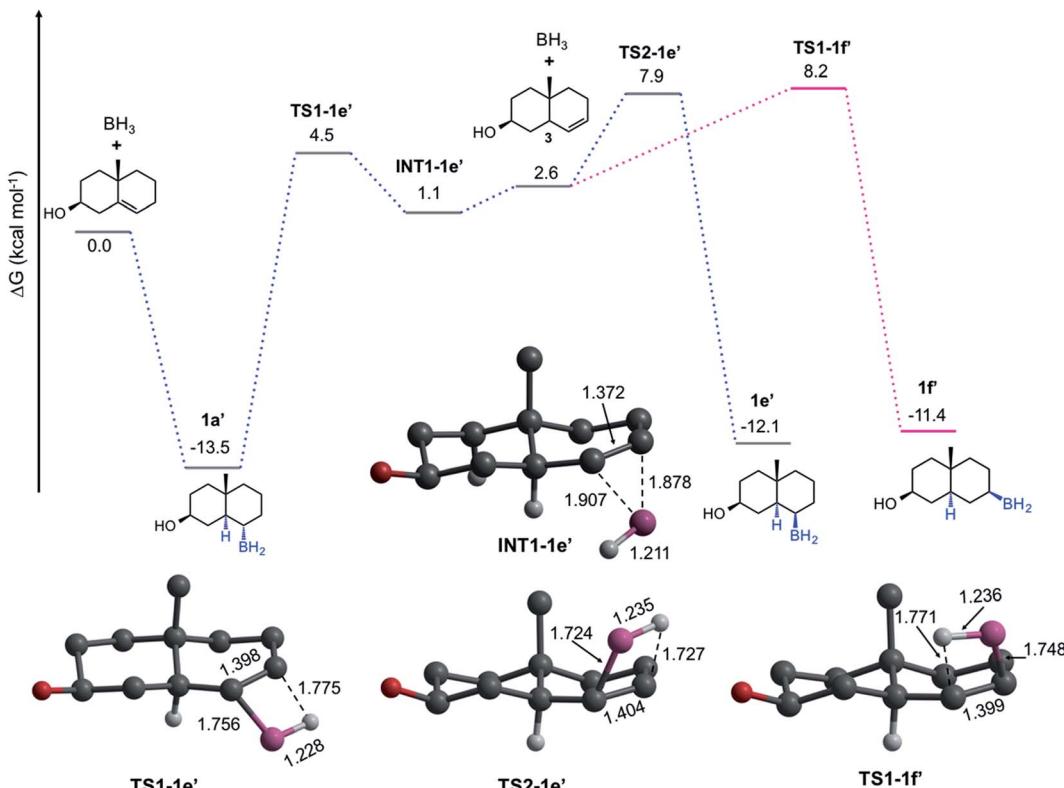


Fig. 4 Gibbs energy profiles (in kcal mol^{-1}) for the formation of **1e'** and **1f'** and transition state structures involved. Bond distances are in Å. In the depicted structures, H atoms are omitted for clarity, except the H atom involved in the hydroboration.

barriers through **TS2-1c'** and **TS2-1d'** are small (1.1 and 2.8 kcal mol^{-1}). However, the barriers for the final step are much higher (7.2 and 8.5 kcal mol^{-1}) and become the rate-limiting steps. This explains why **1d** is not formed, despite having an HB barrier similar to **1b**, and why **1c** is only isolated in traces.

The pathways discussed above are relevant to understand the HB by both α - and β -face, nevertheless, they do not explain the formation of the *trans*-HB product. We hypothesize that the formation of this product involves a *retro*-hydroboration to regenerate the double bond but at C-6 (Fig. 4). This leads to the formation of the Δ^6 -steroid **3** (5 α -cholest-6-en-3 β -ol), followed by typical HB on the β -face. Our computations indicate that **1** is more stable than **3** by 2.6 kcal mol^{-1} . The formation of **3** from **1a'** is concerted *via* **TS1-1e'** ($\Delta G^\ddagger = 18.0 \text{ kcal mol}^{-1}$). The result is the π -complex **INT1-1e'**, which is then converted to the *trans*-product (**1e'**) *via* **TS2-1e'** ($\Delta G^\ddagger = 6.8 \text{ kcal mol}^{-1}$) or to **1f'** *via* **TS1-1f'** (7.1 kcal mol^{-1}). After all the experimental and computational evidence, these results indicate that even though less preferred, a *retro*-hydroboration mechanism is viable under traditional experimental conditions, explaining the formation of **1e**.

Conclusions

In summary, we report the complete characterization of the hydroboration–oxidation products of cholesterol and diosgenin. Because of the steric effect exerted by Me-19, the most

abundant products are the anti-Markovnikov ones by the α -steroidal face. Surprisingly, a *trans*-product is also obtained! This is the first time that such a type of structure is synthesized and characterized under typical hydroboration–oxidation conditions. The best way to explain the formation of this “*trans*-species” is *via* a *retro*-hydroboration of the major product (**a**-type products) to generate the corresponding Δ^6 -structure and the subsequent hydroboration by the β -face. We were lucky to select these steroids as substrates because of the rigidity and different structural environments around the double bond, which allowed us to isolate and characterize the *trans*-product.

Experimental section

General procedure for the hydroboration of Δ^5 -steroids

To a solution of **1** or **2** (2 mmol) in dry THF (30 mL), NaBH_4 (0.38 g, 10 mmol) was added. The system was kept sealed, under stirring, and under argon atmosphere. The reaction mixture was set at the temperature specified in Table 1 before the addition of $\text{BF}_3 \cdot \text{OEt}_2$ (1.65 mL, 13.4 mmol). After stirring for 2 h, the remaining pressure was released, and the work up was performed adding brine (10 mL) dropwise. The THF was evaporated under reduced pressure and the crude product was dissolved in CH_2Cl_2 , washed with brine ($1 \times 50 \text{ mL}$) and water ($3 \times 50 \text{ mL}$), dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The crude mixture was immediately dissolved in a solution of 2% KOH/MeOH (50 mL) and then 5 mL of 35% H_2O_2 were added dropwise. After 1 h of stirring at rt, 200 mL of water

were added, and the resulting precipitate was filtered off and dried under vacuum. The resultant white solids were purified by flash chromatography on a Combiflash apparatus using a gradient elution employing hexane/ethyl acetate (see specific details in the ESI†).

Note: all procedures were carried out employing a commercial 1.0 M solution of $\text{BH}_3\text{-THF}$ and the results were the same.

Author contributions

JCHM, JGM, JSR, and MAFH carried out the experiments. FM, ED, FD, and GM performed the computational studies. MAMH and SB performed the X-ray determinations. All authors interpreted the results and LK, FD, GM, and MAFH prepared the manuscript. All authors have given approval to the final version of the manuscript.

Conflicts of interest

The authors declare no competing financial interest.

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