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Note

Reactions of Diels–Alder adducts of a sugar-derived dihydropyranone leading to fused polycyclic compounds

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Abstract—Manipulation of the ketone and alkene functions of cycloadducts **2**, **3**, and **4**, derived from optically active (ee >86%) (*S*)-2-benzyl-2*H*-pyran-3(6*H*)-one (**1**), led to polycyclic systems having three or four fused rings. Reduction of the carbonyl group of the butadiene adduct (**2**) took place with low facial selectivity affording the alcohols **5** and **6** in 1:1.4 ratio. In contrast, a higher diastereoselection was observed for the reduction of the carbonyl of the cyclopentadiene adducts **3** and **4** to give the *endo* alcohols **10** and **13**, respectively. The epoxidation of **6** showed low facial selectivity in the formation **7** and **8**, whereas epoxidation of **10** and **13** took place from the exo face of the norbornene system to give spontaneously the polycyclic alcohols **11** and **14** by opening of the epoxide by intramolecular attack of the hydroxyl group of the pyranoid ring. Similarly, addition of iodine to **10** led to the polycyclic iodide **12**.

Keywords: Cyclizations; Cycloadducts; Diels–Alder; Dihydropyranones

1. Introduction

The regio- and stereospecific nature of the Diels–Alder reaction has facilitated the construction of complex molecules, mainly natural products.[1,2] Elegant cascade sequences or intramolecular versions of the cycloaddition reaction leads to polycyclic systems,[3] which have been alternatively constructed by manipulation of the usually numerous functionalities of the Diels–Alder cycloadducts.[4] This last approach has succeeded in installing stereocenters with high selectivity and it has been employed for the synthesis of such natural products as (+)-curcudiol,[5] (−)-malyngolide,[6] and conduritols.[7] In connection with these studies we describe here the construction of polycyclic systems by intramolecular cyclizations conducted in optically active cycloadducts. These compounds have been prepared by Diels–Alder addition of butadienes[8] and cyclic dienes[9] to a sugar-derived, chiral dihydropyranone. Several aspects of the chemistry of the cycloadducts as versatile building blocks have been explored. The level of stereocontrol and facial selectivities in reduction, oxidation, and addition reactions were determined. Stereochemical features in the resulting structures are also discussed.

2. Results and discussion

Optically active (*S*)-2-benzyl-2*H*-pyran-3(6*H*)-one (**1**, ee >86%), derived from D-xylose, reacted with butadiene under catalysis by boron trifluoride–ethyl etherate to give the cycloadduct **2** in 81% yield[8] (Scheme 1). To promote the formation of a polycyclic alcohol, compound **2** was subjected to carbonyl reduction and further alkene epoxidation. The reduction of the carbonyl group of **2** was conducted with sodium borohydride, to afford alcohols **5** and **6** (1:1.4 ratio), readily separable by flash chromatography (Scheme 2). The less polar product was identified as **5**, as the $J_{3,4}$ (3.6 Hz) and $J_{4,4a}$ (10.8 Hz) values were consistent with an axial disposition for H-4 (*S* configuration for C-4) in the chair

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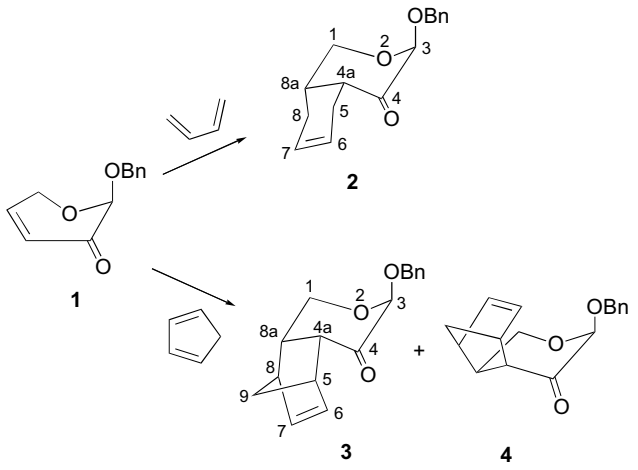
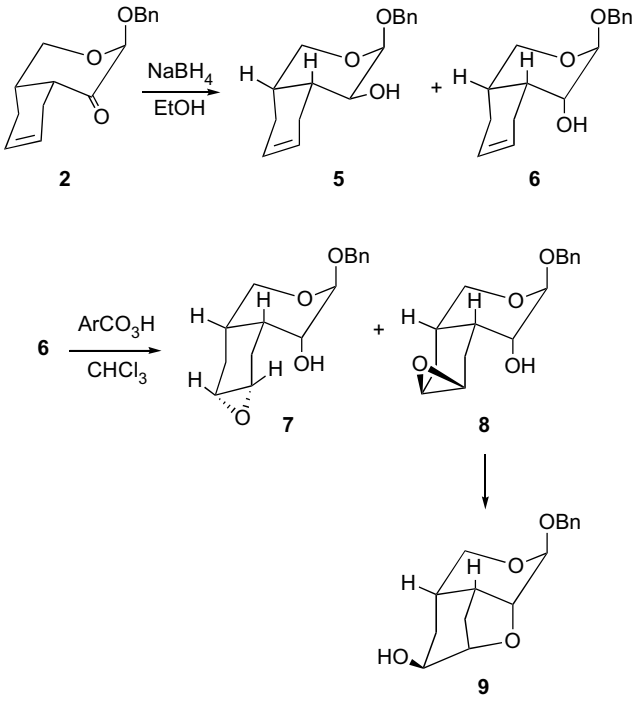


Scheme 1.

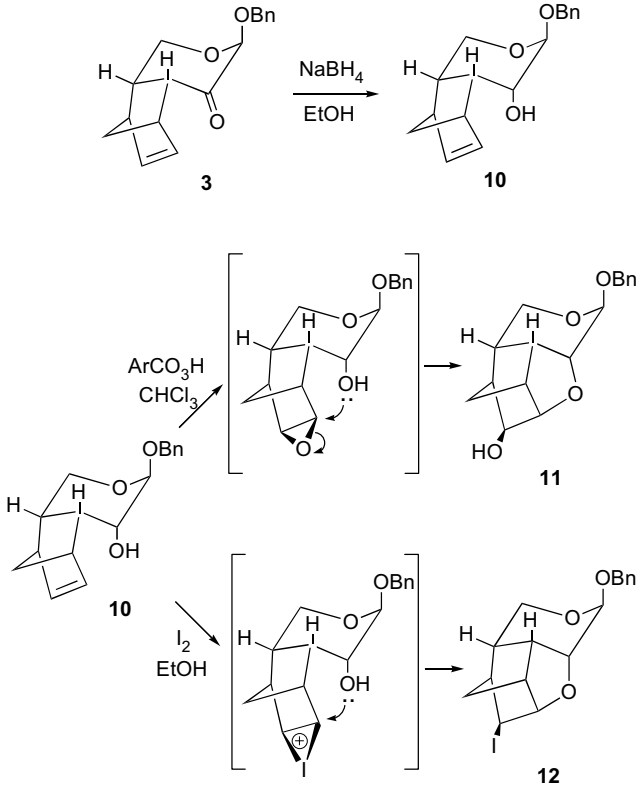


Scheme 2.

conformation of the tetrahydropyran ring that satisfies the anomeric effect.[10] Accordingly, the small values for $J_{1,8a}$ and $J_{1',8a}$ indicated that H-8a is bisecting the angle formed by H-1 and H-1′. The other isomer isolated (**6**) should possess the *R* configuration for the new stereocenter at C-4.

The absolute configuration at C-4 of **5** and **6** was confirmed chemically by oxidation of **6** with *m*-chloroperoxybenzoic acid. The reaction was monitored by TLC and showed formation of two more polar products. When the oxidation was conducted for longer times, a third even more polar product was detected. Separation of the mixture by flash chromatography afforded the stable epoxide **7**, and the next compound isolated, the epoxide **8**, appeared somewhat contaminated with the most polar product. The latter was also isolated and characterized as the polycyclic alcohol **9**, formed by rear side intramolecular attack of the C-4 hydroxyl group on C-6 of the epoxide **8**. In fact, compound **8** completely converts into **9** on standing in a chloroform solution. This chemical transformation has been reported for 5-norbornene-2-*endo*-methanol,[11] which on epoxidation rendered an oxirane ring situated in close proximity to a hydroxyl group. The ^{13}C NMR spectra of **8** and **9** confirmed their structures; for example, the resonances of the carbons C-6 and C-7 (~52 ppm) in **8** underwent a strong downfield shifting in **9** (>70 ppm), as result of the intramolecular epoxide opening by HO-4. Moreover, the incorporation of C-4 into the five-membered tetrahydropyran ring was also evidenced by the deshielding of the C-4 signal in **9**, compared with the same signal in **8**.

The cycloadduct **3**, readily obtained (64% yield) by the $Et_2O{\cdot}BF_3$-promoted cycloaddition of cyclopentadiene to **1**,[9] was subjected to the same sequence of reduction and epoxidation to prepare the corresponding polycyclic alcohol (Scheme 3). Thus, sodium borohydride reduction of **3** was highly diastereoselective in



Scheme 3.

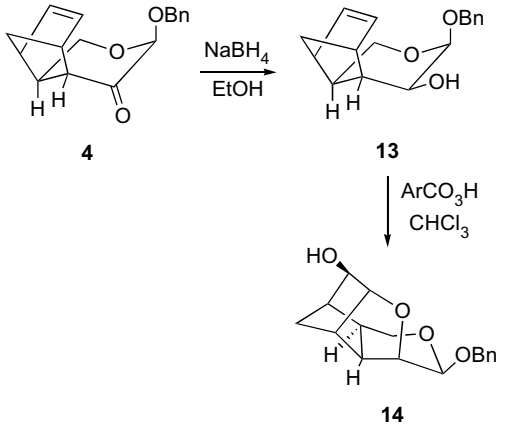
favor of the *endo* alcohol **10** (diastereomeric excess >95%, determined by ^{1}H NMR). The configuration of C-4a in **10** was not evident from the ^{1}H NMR spectrum of the compound, as the presence of the five-membered ring fused to the pyranoid ring produced distorsion of its normal chair conformation,[12,13] and also because the contribution of the opposite chair to the equilibrium, as suggested by the averaging of coupling constants (note, e.g., the averaged values for $J_{1,8a}$ and $J_{1',8a}$). However, as described later, the epoxidation of the olefinic unsaturation of **10** proved conclusively the configuration of the stereocenter at C-4. The high facial diastereoselection in the reduction suggests that the attack by borohydride is more hindered from the α face of the carbonyl, which is *endo* to the bicyclo[2.2.1]hept-2-ene system of **3**. In contrast, the reduction of cyclopentadiene adducts of levoglucosenone[4b,14] and isolevoglucosenone[13,15] was much less stereoselective, indicating that the steric contributions of 1,6-anhydro bridge and the annelated cyclopentene ring have an approximately equal role in deciding the reaction outcome.

The epoxidation of **10** with *m*-chloroperoxybenzoic acid led directly to the polycyclic alcohol **11**, formed by intramolecular nucleophilic attack of the hydroxyl group at C-4 on the epoxide. As the reactive functionalities of **10** were conveniently disposed for the spontaneous cyclization, the intermediate epoxide was detected only as a faint spot by TLC. The analytical and spectral data of **11** were completely consistent with the proposed structure. For example, the $J_{6,7}$ value (~0 Hz) indicated that the two hydrogen atoms are *trans* disposed in the norbornane system.[4b,14] Also, the chemical shifts for the signals of the carbons bonded to oxygen were in good agreement with those found for the polycyclic alcohol **9** and with those of structurally related compounds.[4b,13,14]

In view of the results of the epoxidation–etherification of the double bond of **10**, the electrophilic addition of iodine was attempted. Thus, treatment of **10** with an ethanolic solution of the halogen afforded the crystalline polycyclic iodide **12** as the only reaction product. The ^{1}H NMR spectrum of **12** was very similar to that of **11**, and their ^{13}C NMR spectra were also similar, except for the upfield shift of the carbon bonded to iodine (C-7) in **12**. The addition of iodine to **10** took place by a mechanism analogous to that of the iodolactonization,[16] which consists of the *anti* stereospecific, irreversible back-side opening of an iodonium ion intermediate by the alcohol nucleophile.

The sequence of reduction and epoxidation was also applied to cycloadduct **4**, which was synthesized using $SnCl_4$ or $TiCl_4$ as catalyst for the Diels–Alder addition of cyclopentadiene to **1**.[17] These catalysts promoted the formation of diastereomers (such as **4**) that could not be otherwise obtained in preparative scale in thermally or $Et_2O{\cdot}BF_3$-promoted cycloadditions. Because of the crowding of substituents on the β face of **4**, the reduction with sodium borohydride led to the predictable alcohol **13** as the only detectable product. The structure of **13** was deduced from its ^{1}H NMR spectrum. Thus, the large value for $J_{1'ax,8a}$ (11.8 Hz) indicates a preference for a distorted chair conformation of the pyranoid ring having the benzyloxy group axially oriented, as the magnitude of $J_{3,4}$ (3.2 Hz) agreed with an equatorial–axial disposition for H-3 and H-4, respectively. Epoxidation of **13**, in a manner similar to that employed for norbornene **10**, provided a conclusive demonstration of the configuration of the stereocenters of the starting unsaturated alcohol. As for **10**, the intermediate oxirane ring formed by epoxidation of the double bond of **13** underwent attack by the hydroxyl group to form a five-membered ring. The crowding of substituents on the β face of the pyran results in a distortion of this ring, which is reflected in the small values observed for $J_{1,8a}$ and $J_{3,4}$ (<1 Hz) (Scheme 4).

In summary, the steric hinderance in both the reduction of the carbonyl group and oxidation of the double bond in the cycloadducts account for the diastereoselectivities observed. The high diastereoselection in the reduction of the carbonyl group of **3** and **4** may be attributed to the bulkiness of the vicinal norbornene system that induces the approach of the hydride from the opposite face. The epoxidation of the resulting alcohols **10** and **13** was also highly diastereoselective and took place from the exo face of the double bond. In contrast, a lower selectivity was determined for the reduction of **2** as the cyclohexene ring fused to the pyranone exerts a smaller stereocontrol compared with that of the bicyclo[2.2.1]hept-2-ene system. Similar reasons may be invoked to account for the lower facial selectivity in the epoxidation of **6**, in comparison with the epoxidation of **10** and **13**. Furthermore, the formation of polycyclic systems was also useful to confirm the relative stereochemistry of the reacting groups, as cyclization reactions are only possible when such groups are close in space and have an adequate orientation. The resulting polycyclic



Scheme 4.

systems possess a number of reacting functionalities, and carry a multitude of stereogenic centers that can be installed in a predictable way. In this regard, optically pure polycycles can be prepared starting from enantiomerically pure cycloadducts derived from dihydropyranone analogues of **1** but having an additional chiral center located in the 2-alkoxy substituent.[8,9]

3. Experimental

3.1. General methods

Melting points were determined with a Fisher–Johns apparatus and are uncorrected. Optical rotations were measured at 25 °C with a Perkin–Elmer 343 digital polarimeter. Column chromatographic separations were performed with Silica Gel 60, 240–400 mesh. Analytical TLC was conducted on Silica Gel 60 F_{254} precoated plates (0.2 mm). Visualization of the spots was effected by exposure to UV light and charring with a solution of 5% H_2SO_4 in EtOH, containing 0.5% *p*-anisaldehyde. Solvents were reagent grade and, in most cases, were dried and distilled prior to use according to standard procedures. Nuclear magnetic resonance (NMR) spectra were recorded with a Bruker AM 500 instrument, in $CDCl_3$ solutions using Me_4Si as an internal standard. The identity of the protons in the ^1H NMR spectra of the products was confirmed by 2D COSY NMR experiments; and for the assignment of the signals in the ^{13}C NMR spectra, DEPT experiments were conducted.

3.2. (3*S*,4*S*,4a*R*,8a*S*)-3-Benzyloxy-4-hydroxy-3,4,4a,5,8,8a-hexahydro-1*H*-2-benzopyran (5) and its (4*R*)-isomer (6)

A solution of **2**[8] (0.66 g, 2.55 mmol, ee >86%) in 96% EtOH (25 mL) was cooled to 0 °C and $NaBH_4$ (0.11 g, 2.91 mmol) was added. The mixture was stirred at 0 °C during 15 min, when TLC (6:1 hexane–EtOAc) showed complete conversion of **2** (R_f 0.63) into two more polar products (R_f 0.45 and 0.33). The mixture was diluted with MeOH and concentrated. This procedure was repeated three times, and the residue was dissolved in CH_2Cl_2 (50 mL). The organic solution was washed with saturated (satd) aqueous (aq) NaCl, dried ($MgSO_4$), and concentrated. The resulting syrup was purified by flash chromatography with 45:1 hexane–EtOAc to afford compound **5** (0.22 g, 33%); mp 60 °C; $[\alpha]_D^{25}$ −101.4° (*c* 1.0, $CHCl_3$) (this value corresponded to an ee >86%); ^1H NMR (500 MHz, $CDCl_3$+D_2O) δ 7.36 (m, 5H, H-aromatic), 5.69, 5.61 (m, 2, H-6,7), 4.92 (d, 1, $J_{3,4}$ 3.6 Hz, H-3), 4.81, 4.51 (2d, 2H, *J* 11.6 Hz, PhCH_2O), 3.96 (dd, 1H, $J_{1,1'}$ 11.0 Hz, $J_{1,8a}$ 1.9 Hz, H-1), 3.60 (dd, 1H, $J_{4,4a}$ 10.8 Hz, H-4), 3.34 (d, 1H, $J_{1',8a} \sim 0$ Hz, H-1′), 2.44–1.90 (m, 6H, H-4a,5,5′,8,8′,8a); ^{13}C NMR (50.3 MHz, $CDCl_3$+D_2O) δ 137.6, 128.5, 128.0, 127.9 (C-aromatic), 125.5, 124.3 (C-6,7), 97.8 (C-3), 69.4 (PhC_2O), 66.4 (C-4), 63.8 (C-1), 34.1 (C-4a), 32.4 (C-8a), 24.7, 24.3 (C-5,8). Anal. Calcd for $C_{16}H_{20}O_3$: C, 73.82; H, 7.74. Found: C, 73.50; H, 8.01.

Elution of the column with 30:1 hexane–EtOAc gave the more polar product **6** (0.35 g, 53%, ee >86%); $[\alpha]_D^{25}$ −92.0° (*c* 1.0, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$+D_2O) δ 7.35 (br s, 5H, H-aromatic), 5.73, 5.69 (m, 2H, H-6,7), 4.87, 4.55 (2d, 2H, *J* 11.8 Hz, PhCH_2O), 4.68 (d, 1H, $J_{3,4}$ 5.4 Hz, H-3), 3.79 (dd, 1H, $J_{1,1'}$ 11.4 Hz, $J_{1,8a}$ 3.7 Hz, H-1), 3.62 (dd, 1H, $J_{4,4a}$ 4.6 Hz, H-4), 3.52 (dd, 1H, $J_{1',8a}$ 7.7 Hz, H-1′), 2.41–2.04 (m, 6H, H-4a,5,5′,8,8′,8a); ^{13}C NMR (50.3 MHz, $CDCl_3$+D_2O) δ 137.5, 128.5, 128.1, 127.9 (C-aromatic), 125.7, 125.2 (C-6,7), 99.7 (C-3), 72.1 (C-4), 70.2 (PhC_2O), 64.9 (C-1), 32.4, 31.6 (C-4a,8a), 26.1, 23.3 (C-5,8). Anal. Calcd for $C_{16}H_{20}O_3$: C, 73.82; H, 7.74. Found: C, 73.99; H, 7.76.

The diastereoselectivity of this reaction was established from the ^1H NMR spectrum of the crude mixture, which showed a 1.0:1.4 ratio for **5**:**6**.

3.3. (3*S*,4*R*,4a*R*,6*S*,7*R*,8a*S*)-3-Benzyloxy-6,7-epoxy-4-hydroxyperhydro-1*H*-2-benzopyran (7), its (6*R*,7*S*) isomer (8), and the polycylic alcohol 9

To a solution of **6** (0.15 g, 0.58 mmol, ee >86%) in $CHCl_3$ (4 mL) was added a solution of *m*-chloroperoxybenzoic acid (80% purity; 0.20 g, 0.93 mmol) in $CHCl_3$ (4 mL). The mixture was stirred at room temperature for 20 min, when TLC (1:1 hexane–EtOAc) indicated the absence of **6** and the formation of two lower moving products (R_f 0.41 and 0.38) and a third spot (R_f 0.25), which became more intense when the reaction was conducted for longer times. The mixture was diluted with CH_2Cl_2 and washed with satd aq $NaHCO_3$, dried ($MgSO_4$), and concentrated. The residue was subjected to flash chromatography with 4:1 hexane–EtOAc. The less polar component was identified as the oxirane derivative **7** (85 mg, 53%, ee >86%); $[\alpha]_D^{25}$ −70.5° (*c* 1.0, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 7.33 (m, 5H, H-aromatic), 4.75 (d, 1H, $J_{3,4}$ 2.1 Hz, H-3), 4.75, 4.51 (2d, 2H, *J* 11.6 Hz, PhCH_2O), 3.96 (dd, 1H, $J_{1,1'}$ 11.4 Hz, $J_{1,8a}$ 3.4 Hz, H-1), 3.49 (dd, 1H, $J_{4,4a}$ 3.2 Hz, H-4), 3.45 (dd, 1H, $J_{1',8a}$ 2.4 Hz, H-1′), 3.37 (dd, 1H, $J_{6,7}$ 4.0 Hz, $J_{7,8} < 1$ Hz, $J_{7,8'}$ 5.8 Hz, H-7), 3.25 (ddd, 1H, $J_{5,6}$ 2.7 Hz, $J_{5',6} \sim 1.4$ Hz, H-6), 2.34 (dd, 1H, $J_{8,8'}$ 16.0 Hz, $J_{8,8a}$ 11.6 Hz, H-8), 2.33 (dd, 1H, $J_{4a,5}$ 8.0 Hz, $J_{4a,5'}$ 2.8 Hz, $J_{4a,8a}$ 6.0 Hz, H-4a), 2.21 (ddd, 1H, $J_{5,5'}$ 16.4 Hz, H-5), 2.16 (ddd, 1H, H-5′), 1.96 (ddd, 1H, $J_{8',8a}$ 7.0 Hz, H-8′), 1.51 (dddd, 1H, H-8a); ^{13}C NMR (50.3 MHz, $CDCl_3$) δ 137.6, 128.4, 127.9, 127.7 (C-aromatic), 99.0 (C-3), 69.3 (C-4), 69.1 (PhC_2O), 63.0 (C-1), 53.1, 51.3 (C-6,7), 30.0, 28.6 (C-4a,8a), 26.5, 24.4 (C-5,8). Anal. Calcd for $C_{16}H_{20}O_4$: C, 69.55; H, 7.29. Found: C, 69.68; H, 7.49.

From the next fractions of the column was isolated the epoxide **8** (9 mg, 6%) somewhat contaminated with the more polar product; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.34 (m, 5H, H-aromatic), 4.79, 4.51 (2d, 2H, J 11.8 Hz, PhCH_2O), 4.68 (d, 1H, $J_{3,4}$ 3.9 Hz, H-3), 3.85 (dd, 1H, $J_{1,1'}$ 11.4 Hz, $J_{1,8a}$ 3.8 Hz, H-1), 3.53 (t, 1H, $J_{4,4a}$ 3.9 Hz, H-4), 3.43 (dd, 1H, $J_{1',8a}$ 5.2 Hz, H-1′), 3.23 (br t, 1H, $J_{6,7} \sim J_{7,8'} \sim 4.0$ Hz, H-7), 3.21 (m, 1H, H-6), 2.24 (dd, 1H, $J_{8,8'}$ 15.5 Hz, $J_{8,8a}$ 8.2 Hz, H-8), 2.18 (m, 1H, H-4a), 2.11 (ddd, 1H, $J_{4a,5}$ 8.2 Hz, $J_{5,5'}$ 15.5 Hz, $J_{5,6}$ 2.7 Hz, H-5), 2.05 (ddd, 1H, $J_{4a,5'}$ 1.4 Hz, $J_{5',6}$ 6.6 Hz, H-5′), 1.88 (dt, 1H, $J_{8',8a} \sim 4.0$ Hz, H-8′), 1.82 (m, 1H, H-8a); ^{13}C NMR (50.3 MHz, $CDCl_3$) δ 137.4, 128.5, 128.0, 127.9 (C-aromatic), 99.6 (C-3), 71.9 (C-4), 69.5 (PhC_2O), 64.3 (C-1), 52.9, 51.8 (C-6,7), 28.5, 28.1 (C-4a,8a), 25.6, 23.9 (C-5,8).

Upon elution of the column with mixtures of increasing polarity of hexane–EtOAc (from 4:1 to 2:1) the more polar product was isolated and identified as the polycyclic alcohol **9** (34 mg, 21%, ee >86%); $[\alpha]_D^{25}$ −67.4° (c 1.4, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.34 (m, 5H, H-aromatic), 4.94 (br s, 1H, H-3), 4.75, 4.52 (2d, 2H, J 11.8 Hz, PhCH^2O), 4.13 (dd, 1H, $J_{5',6}$ 6.1 Hz, $J_{6,7}$ 3.2 Hz, H-6), 4.06 (ddd, 1H, $J_{7,8}$ 7.1 Hz, $J_{7,8'}$ 3.7 Hz, H-7), 3.88 (dd, 1H, $J_{1,1'}$ 11.2 Hz, $J_{1,8a}$ 2.1 Hz, H-1), 3.70 (d, 1H, $J_{4,4a}$ 3.6 Hz, H-4), 3.27 (dd, 1H, $J_{1',8a}$ 1.8 Hz, H-1′), 2.42 (m, 1H, H-4a), 2.19 (ddd, 1H, $J_{8,8'}$ 15.0 Hz, $J_{8,8a}$ 6.0 Hz, H-8), 2.17 (d, 1H, $J_{4a,5} < 1$ Hz, $J_{5,5'}$ 11.6 Hz, H-5), 1.97 (m, 1H, H-8a), 1.75 (ddd, 1H, $J_{4a,5'} \sim 5.5$ Hz, H-5′), 1.54 (ddd, 1H, $J_{8',8a}$ 9.8 Hz, H-8′); ^{13}C NMR (50.3 MHz, $CDCl_3$) δ 137.7, 128.4, 128.0, 127.8 (C-aromatic), 95.8 (C-3), 78.6 (C-6), 76.2 (C-4), 70.4 (C-7), 69.0 (PhC_2O), 63.0 (C-1), 32.7 (C-4a), 29.9, 29.8 (C-5,8), 28.1 (C-8a). Anal. Calcd for C_{16} $H_{20}O_4$: C, 69.55; H, 7.29. Found: C, 69.83; H, 7.38.

On standing at room temperature, oxirane **8** in $CHCl_3$ solution underwent almost quantitative conversion into the polycyclic alcohol **9**. The diastereoselectivity of the reaction, determined from the ^{1}H NMR spectrum of the crude mixture after complete conversion of **8** into **9**, showed a 1.9:1.0 ratio for **7**:**9**.

3.4. (3*S*,4*R*,4a*R*,5*S*,8*R*,8a*S*)-3-Benzyloxy-4-hydroxy-3,4,4a,5,8,8a-hexahydro-5,8-methano-1*H*-2-benzopyran (10)

The ketone group of **3**[9] (0.55 g, 2.03 mmol, ee >86%) was reduced with $NaBH_4$ (95 mg, 2.51 mmol) as previously described for the reduction of **2**. After 15 min TLC (3:1 hexane–EtOAc) showed complete consumption of the starting **3** (R_f 0.40) and formation of a more polar product (R_f 0.23). The usual workup of the reaction mixture followed by chromatographic purification led to the *endo* alcohol **10** (0.46 g, 83%, ee >86%) as an amorphous solid; $[\alpha]_D^{25}$ −103.4° (c 1.1, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.32 (br s, 5H, H-aromatic), 6.18, 6.11 (2dd, 2H, $J_{6,7}$ 5.6 Hz, $J_{5,6} \sim J_{7,8} = 3.0$ Hz, H-6,7), 4.77, 4.44 (2d, 2H, J 11.7 Hz, PhCH_2O), 4.35 (d, 1H, $J_{3,4}$ 6.5 Hz, H-3), 3.97 (dd, 1H, $J_{1,1'}$ 11.9 Hz, $J_{1,8a}$ 5.8 Hz, H-1), 3.94 (dd, 1H, $J_{4,4a}$ 7.8 Hz, H-4), 3.51 (dd, 1H, $J_{1',8a}$ 4.9 Hz, H-1′), 3.01, 2.82 (2br s, 2H, H-5,8), 2.75 (ddd, 1H, $J_{4a,5}$ 3.5 Hz, $J_{4a,8a}$ 10.4 Hz, H-4a), 2.59 (m, 1H, $J_{8,8a} \sim 4.0$ Hz, H-8a), 1.76 (br s, 1H, *H*O), 1.47 (br d, 1H, $J_{9,9'}$ 8.2 Hz, H-9), 1.34 (br d, 1H, H-9′); ^{13}C NMR (50.3 MHz, $CDCl_3$) δ 137.9, 128.4, 127.9, 127.7 (C-aromatic), 135.8, 134.5 (C-6,7), 100.5 (C-3), 70.3 (C-4), 69.6 (PhC_2O), 63.8 (C-1), 51.1 (C-9), 46.5, 44.8, 40.5, 39.4 (C-4a,5,8,8a). Anal. Calcd for $C_{17}H_{20}O_3$: C, 74.97; H, 7.40. Found: C, 75.29; H, 7.07.

3.5. Conversion of 10 into the polycyclic alcohol 11

A solution of **10** (105 mg, 0.39 mmol, ee >86%) in $CHCl_3$ (4 mL) was treated with a solution of *m*-chloroperoxybenzoic acid (80% purity, 150 mg, 0.70 mmol) in $CHCl_3$ (4 mL). The mixture was stirred at room temperature for 5 min, when TLC (2:1 hexane–EtOAc) showed no starting material (**10**; R_f 0.52) remaining and the formation of a lower migrating product (R_f 0.29). This compound was gradually converted into an even more polar product (R_f 0.14), which was the major one detected by TLC after 3 h of reaction. The mixture was diluted with CH_2Cl_2, washed with satd aq $NaHCO_3$, dried ($MgSO_4$), and concentrated. The product having R_f 0.14 was isolated by flash chromatography (2.5:1 hexane–EtOAc) and identified as the polycyclic alcohol **11** (93 mg, 84%, ee >86%); mp 137 °C; $[\alpha]_D^{25}$ −58.3° (c 1.1, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$+D_2O) δ 7.33 (br s, 5H, H-aromatic), 4.80 (d, 1H, $J_{3,4}$ 1.6 Hz, H-3), 4.72, 4.49 (2d, 2H, J 11.8 Hz, PhCH_2O), 4.20 (br s, 1H, $J_{6,7} \sim 0$ Hz, H-7), 4.07 (dd, 1H, $J_{1,1'}$ 12.3 Hz, $J_{1,8a}$ 5.5 Hz, H-1ax), 4.04 (d, 1H, $J_{5,6}$ 4.8 Hz, H-6), 3.92 (dd, 1H, $J_{4,4a}$ 5.3 Hz, H-4), 3.72 (d, 1H, $J_{1',8a} \sim 0$ Hz, H-1′eq), 2.82 (ddd, 1H, $J_{4a,5}$ 5.1 Hz, $J_{5,9}$ 1.2 Hz, H-5), 2.49 (ddd, 1H, $J_{4a,8a}$ 10.2 Hz, H-4a), 2.12 (br s, 1H, H-8), 1.92 (br d, 1H, $J_{8,9} \sim 1.4$ Hz, $J_{9,9'}$ 10.7 Hz, H-9), 1.74 (ddd, 1H, $J_{8,8a}$ 3.9 Hz, H-8a), 1.38 (br d, 1H, H-9′); ^{13}C NMR (50.3 MHz, $CDCl_3$+D_2O) δ 137.4, 128.5, 127.9, 127.8 (C-aromatic), 95.3 (C-3), 88.9 (C-6), 76.4, 76.2 (C-4,7), 69.1 (PhC_2O), 58.2 (C-1), 48.0, 46.7 (C-5,8), 32.9, 32.7 (C-4a,8a), 31.8 (C-9). Anal. Calcd for $C_{17}H_{20}O_4$: C, 70.81; H, 6.99. Found: C, 70.48; H, 6.86.

3.6. Conversion of 10 into the polycyclic iodide 12

A solution of iodine (0.12 g, 0.47 mmol) in 96% EtOH (7 mL) was added dropwise to a solution of **10** (0.10 g, 0.37 mmol, ee >86%) in 96% EtOH (7 mL). After 30 min of stirring at room temperature, the mixture showed by TLC (2:1 hexane–EtOAc) complete conversion of **10** (R_f 0.52) into a less polar product (R_f 0.68). The solution was concentrated and the residue diluted with CH_2Cl_2.

The organic solution was washed with satd aq $Na_2S_2O_3$, dried ($MgSO_4$), and concentrated. The residue was purified by flash chromatography (50:1 hexane–EtOAc) to afford **12** (0.12 g, 81%, ee >86%) as a colorless, crystalline solid; mp 126 °C; $[\alpha]_D^{25}$ −18.9° (*c* 1.1, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.33 (br s, 5H, H-aromatic), 4.80-4.79 (m, 2H, H-3,6), 4.71, 4.50 (2d, 2H, *J* 11.8 Hz, PhCH_2O), 4.42 (d, 1H, $J_{6,7} \sim 0$ Hz, $J_{7,9'}$ 2.5 Hz, H-7), 4.08 (dd, 1H, $J_{1,1'}$ 12.5 Hz, $J_{1,8a}$ 5.2 Hz, H-1ax), 3.89 (dd, 1H, $J_{3,4}$ 1.7 Hz, $J_{4,4a}$ 5.4 Hz, H-4), 3.73 (d, 1H, $J_{1',8a} \sim 0$ Hz, H-1′eq), 2.79 (ddd, 1H, $J_{4a,5}$ 5.1 Hz, $J_{5,6}$ 4.8 Hz, $J_{5,9}$ 1.3 Hz, H-5), 2.54 (ddd, 1H, $J_{4a,8a}$ 10.0 Hz, H-4a), 2.44 (br s, 1H, H-8), 2.11 (br d, 1H, $J_{8,9}$ 1.1 Hz, $J_{9,9'}$ 10.9 Hz, H-9), 1.86 (ddd, 1H, $J_{8,8a}$ 3.7 Hz, H-8a), 1.65 (br d, 1H, H-9′); ^{13}C NMR (50.3 MHz, $CDCl_3$) δ 137.3, 128.5, 128.0, 127.9 (C-aromatic), 95.0 (C-3), 90.8 (C-6), 75.7 (C-4), 69.2 (PhC_2O), 58.1 (C-1), 50.0 (C-5), 49.9 (C-8), 36.3 (C-9), 35.0 (C-8a), 33.2 (C-7), 32.8 (C-4a). Anal. Calcd for $C_{17}H_{19}IO_3$: C, 51.27; H, 4.81; I, 31.87. Found: C, 51.69; H, 4.92; I, 31.46.

3.7. (3*S*,4*S*,4a*S*,5*R*,8*S*,8a*R*)-3-Benzyloxy-4-hydroxy-3,4,4a,5,8,8a-hexahydro-5,8-methano-1*H*-2-benzopyran (13)

The ketone group of **4**[17] (0.33 g, 1.22 mmol, ee >86%) was reduced with $NaBH_4$ (57 mg, 1.51 mmol) as previously described for the reduction of **3**. After 1 h, the usual workup of the reaction mixture followed by chromatographic purification led to alcohol **13** (0.29 g, 87%, ee >86%) as an amorphous solid; $[\alpha]_D^{25}$ −57.3° (*c* 1.1, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$+D_2O) δ 7.33 (br s, 5H, H-aromatic), 6.26, 5.87 (2dd, 2H, $J_{6,7}$ 5.6 Hz, $J_{5,6} \sim J_{7,8} = 3.1$ Hz, H-6,7), 4.85, 4.57 (2d, 2H, *J* 11.9 Hz, PhCH_2O), 4.65 (dd, 1H, $J_{3,4}$ 3.2 Hz, H-3), 4.08 (dd, 1H, $J_{4,4a}$ 5.6 Hz, H-4), 3.74 (ddd, 1H, $J_{1,1'}$ 10.2 Hz, $J_{1,8a}$ 6.2 Hz, H-1eq), 3.50 (dd, 1H, $J_{1',8a}$ 11.8 Hz, H-1′ax), 3.01 (br s, 1H, H-5), 2.76 (br s, 1H, H-8), 2.52 (dddd, 1H, $J_{4a,8a}$ 10.0 Hz, $J_{5,8a}$ 3.6 Hz, H-8a), 2.27 (ddd, 1H, $J_{4a,5}$ 3.4 Hz, H-4a), 1.50 (dt, 1H, $J_{5,9} \sim J_{8,9} = 1.8$ Hz, $J_{9,9'}$ 8.0 Hz, H-9), 1.37 (br d, 1H, H-9′); ^{13}C NMR (50.3 MHz, $CDCl_3$) δ 137.9, 131.1 (C-6,7), 137.8, 128.4, 127.9, 127.7 (C-aromatic), 95.7 (C-3), 69.2 (PhC_2O), 68.0 (C-4), 65.0 (C-1), 51.3 (C-9), 45.6, 44.1, 40.7, 39.7 (C-4a,5,8,8a). Anal. Calcd for $C_{17}H_{20}O_3$: C, 74.97; H, 7.40. Found: C, 75.09; H, 7.39.

3.8. Conversion of 13 into the polycyclic alcohol 14

A solution of **13** (103 mg, 0.38 mmol, ee >86%) in $CHCl_3$ (4 mL) was treated with a solution of *m*-chloroperoxybenzoic acid (80% purity, 150 mg, 0.70 mmol) in $CHCl_3$ (4 mL). After 3 h, the usual workup of the reaction mixture followed by chromatographic purification led to the polycyclic alcohol **14** (71 mg, 65%, ee >86%); $[\alpha]_D^{25}$ −43.9° (*c* 1.2, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$+D_2O) δ 7.33 (m, 5H, H-aromatic), 4.90, 4.64 (2d, 2H, *J* 12.5 Hz, PhCH_2O), 4.32 (br s, 1H, $J_{6,7} \sim 0$ Hz, H-7), 4.24 (br s, 1H, $J_{3,4} \sim 0$ Hz, H-3), 4.18 (d, 1H, $J_{1,1'}$ 12.8 Hz, $J_{1,8a} < 1$ Hz, H-1eq), 4.16 (d, 1H, $J_{5,6}$ 4.7 Hz, H-6), 4.02 (d, 1H, $J_{4,4a}$ 5.2 Hz, H-4), 3.77 (dd, 1H, $J_{1',8a}$ 5.2 Hz, H-1′ax), 2.78 (br dt, 1H, $J_{4a,5}$ 5.0 Hz, $J_{5,9'}$ 1.1 Hz, H-5), 2.43 (ddd, 1H, $J_{4a,8a}$ 10.0 Hz, H-4a), 2.12 (br s, 1H, H-8), 1.95 (d, 1H, $J_{9,9'}$ 10.6 Hz, H-9), 1.66 (ddd, 1H, $J_{8,8a} \sim 4.0$ Hz, H-8a), 1.36 (br dd, 1H, H-9′); ^{13}C NMR (50.3 MHz, $CDCl_3$+D_2O) δ 137.4, 128.3, 128.2, 127.7 (C-aromatic), 98.7 (C-3), 89.1 (C-6), 77.1, 76.2 (C-4,7), 70.0 (PhC_2O), 66.1 (C-1), 47.5, 46.2 (C-5,8), 38.8, 34.1 (C-4a,8a), 32.6 (C-9). Anal. Calcd for $C_{17}H_{20}O_4$: C, 70.81; H, 6.99. Found: C, 70.45; H, 6.97.

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