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Note

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Synthesis and Chiroptical Properties of Arylimines of Cholest-4-ene-3,6-dione

Xin Geng, Joel T. Mague, and Robert A. Pascal, Jr.*

Department of Chemistry, Tulane University, New Orleans, LA 70118, USA

E-mail: rpascal@tulane.edu

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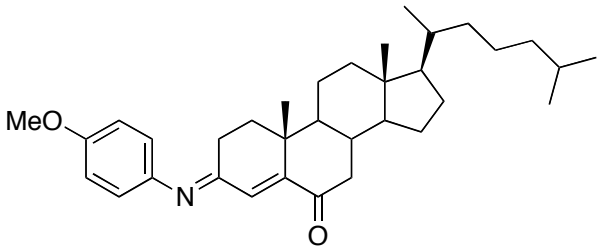
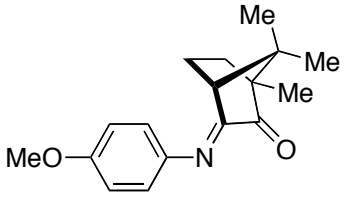


Abstract: In the hope of generating a new class of materials with large optical rotations, various arylamines were condensed with cholest-4-ene-3,6-dione (**2**) to give 3-arylimino steroids. These compounds possess moderately high specific rotations ($[\alpha]_D$ ~ 300-800) and strong circular dichroism. One such derivative, 3-(4-methoxyphenylimino)cholest-4-en-6-one (**3**), crystallizes as the (*E*)-imine, and upon dissolution undergoes mutarotation to an equilibrium mixture of (*E*)- and (*Z*)-isomers with a half-life of approximately one hour at room temperature, as judged by both NMR spectroscopy and polarimetry.

Our long-standing interest in twisted polycyclic aromatic compounds[1] eventually led to the preparation of resolvable twisted acenes (9,10,11,20,21,22-hexaphenyltetrabenzo[*a*,*c*,*l*,*n*]-pentacene and a dimethyl derivative), which exhibited exceptionally high specific rotations ($[\alpha]_D$ ~ 5000-7500).[2] Unfortunately, these compounds are not configurationally stable at room temperature. We subsequently prepared a number of configurationally stable twisted acenes, but these proved to have relatively modest specific rotations.[3] In any event, the synthetic yields of such sterically crowded, polycyclic aromatics are at best fair, so that if one wished to employ compounds of high specific rotation in materials science applications, one would have to look elsewhere. For such a purpose, the various helicene quinones of Katz and coworkers are one class of high-rotation compounds that may be prepared in multigram quantities,[4] but even these syntheses are not "simple". Indeed, the most easily accessible high-rotation compounds remain the aryliminocamphors of Forster and Thornley (e.g., compound **1**, $[\alpha]_D$ –1223), prepared by condensation of aniline derivatives with readily available camphorquinone.[5]



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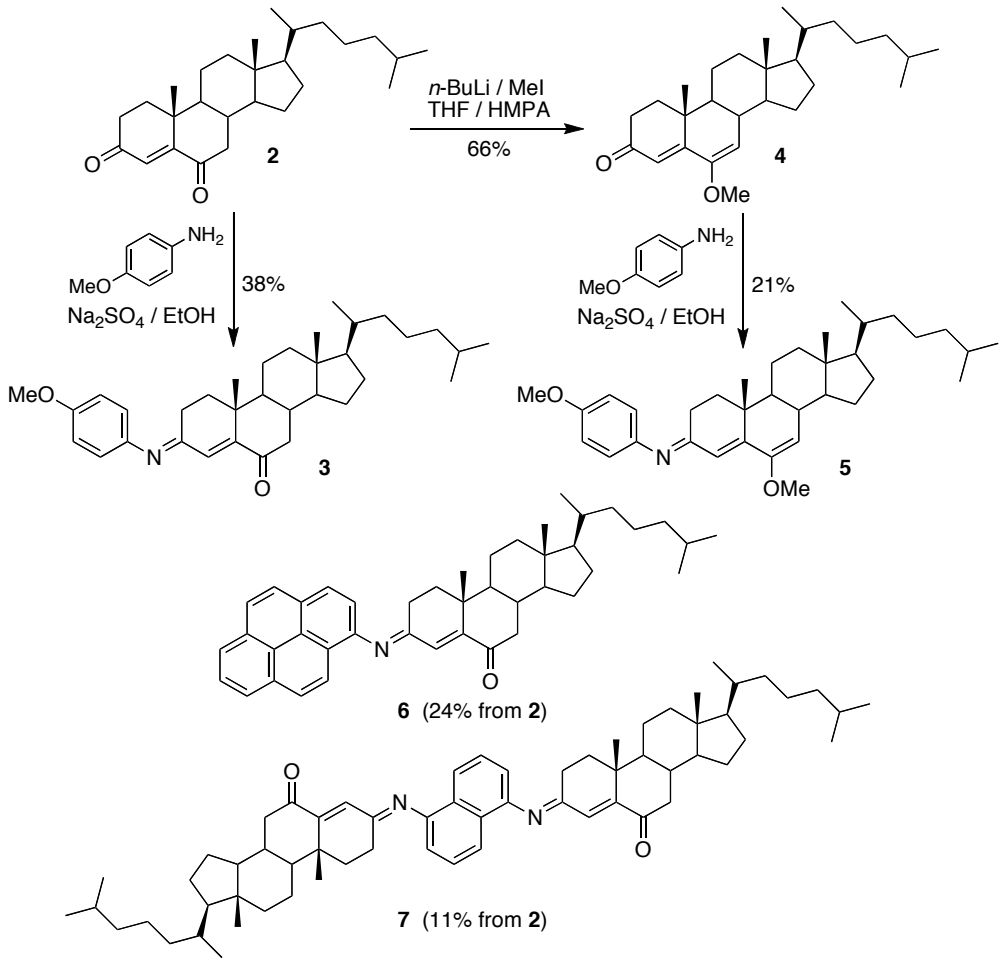
We wondered if there might be other diketones, trivially derived from common natural products, that would provide the basis for a new series of high-rotation materials. Steroid diketones are an obvious possibility, and a few minutes spent browsing Fieser's *Steroids*[6] revealed several candidates. Cholest-4-ene-3,6-dione (**2**, Scheme 1), prepared in high yield by dichromate oxidation of cholesterol without the need for chromatography,[7] was judged to be the best compound for an initial investigation after DFT calculations of an arylimino derivative indicated that it might possess $[\alpha]_D > 1000$. We report herein the synthesis and chiroptical properties of several arylimino derivatives of compound **2**, and we compare these data to the results of DFT calculations.

The condensation of aryl amines with diketone **2** was straightforward, but chromatographic purification of the product was required in all cases. The general method was to mix the steroid, amine or diamine, and anhydrous Na_2SO_4 in ethanol in a screw-capped tube, and then to place the tube in a boiling water bath (100 °C) or an oil bath (120 °C) for 1-48 h. Concentration and chromatography gave the desired imines **3**, **6**, and **7** in modest yields (Scheme 1). An attempt to methylate compound **2** at C-2, in order to limit the available conformations of the derived imines (see below), gave mainly the 6-O-methylated product **4**. Compound **4** was condensed with *p*-anisidine, to give imine **5**.

Scheme 1



In principle, either the C-3 or the C-6 carbonyl group of compound **2** might react to form imines, and although the C-3 carbonyl is presumed to be more reactive, the NMR spectra of the

products do not unambiguously establish the regioselectivity of the condensation. Fortunately, compound **3** is highly crystalline (the other imines are not), and ultimately its X-ray structure was determined. The structure contains two crystallographically independent molecules of **3**, and both crystallize as the (*E*)-imine of the C-3 carbonyl group. The molecular structure of one of these molecules is illustrated in Figure 1.

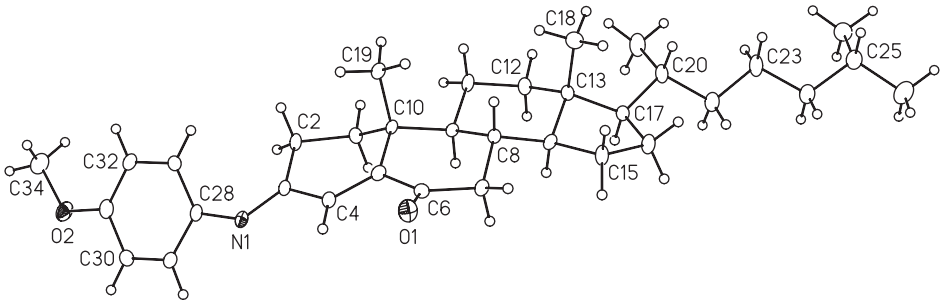


Figure 1. Molecular structure of compound **3**; thermal ellipsoids are drawn at the 50% probability level.

The imines synthesized in this study proved to consist of a mixture of (*E*)- and (*Z*)-isomers at the imine bond, and these isomers only slowly interconvert at room temperature. As a result, these compounds tend to be poorly crystalline, if at all. An exception is compound **3**, which readily forms golden needles from ethanol, and which was shown to contain only the (*E*)-isomer by X-ray analysis. Long before the crystal structure was determined, we noticed that when proton NMR spectra of compound **3** were recorded shortly after dissolution in $CDCl_3$, the spectrum showed only a single olefinic resonance (δ 6.70) and a single methoxy resonance (δ 3.80). However, if a sample was left overnight before recording the spectrum, then two olefin and two methoxy resonances were visible in an approximately 3:2 ratio, with the originally observed resonances still predominant. Because the exclusive isomer in the NMR spectrum of freshly dissolved **3** remains the major isomer after equilibration, the (*E*)-isomer is demonstrated to be the lowest energy stereoisomer. In a kinetic study, the isomerization of compound **3** was monitored by integration of the NMR spectra over several hours. The isomerization proved to be a simple first-order process (see the Supporting Information) with a half-life of 53.5 min at 19

°C, yielding $\Delta G^{\ddagger}$ = 22.0 kcal/mol. This value is in good agreement with reported barriers for imine rotation, although these can vary significantly, depending on the substituents present.[8]

With a variety of imines in hand, the specific rotations ($[\alpha]_D$) of all compounds were recorded in chloroform solution at ambient temperature. These data are found in Table 1. Circular dichroism (CD) spectra were also recorded in chloroform solution, and the spectra are illustrated in the Supporting Information. The specific rotations these of imines are high, but not exceptionally so, with no measured $[\alpha]_D$ greater than 800. As seen from the computational studies described below, the relatively modest rotations are due to the presence of accessible conformations with both high positive and high negative rotatory power.

Table 1. Experimental and Calculated Specific Rotations for Compounds **3**, **5**, **6**, and **7**.

cmpd	**3**	**5**	**6**	**7**
$[\alpha]_D$ (exptl)	+763 (3 min) **+581** (3 h)	**+412**	**+552**	**+271**
$[\alpha]_D$ (calcd) [ΔE][a]				
conf A[b]	+1404 [+0.8]	+1216 [+0.4]	+2322 [+0.4]	+2291 [+0.7][c]
conf Ac[b]	+1131 [+0.7]	+928 [+0.3]		
conf B	–1207 [+0.9]	–944 [+0.7]	–1780 [+0.5]	–1437 [+1.5][c]
conf Bc	–1020 [+1.0]	–715 [+0.6]		
conf C	–1096 [+1.0]	–736 [+0.4]	–2025 [+0.4]	–1377 [+1.2][c]
conf Cc	–727 [+0.7]	–369 [+0.5]		
conf D	+1112 [0.0]	+802 [0.0]	+1985 [0.0]	+1127 [0.0][c]
conf Dc	+869 [+0.2]	+525 [+0.1]		
Boltzmann-weighted sum	**+609**	**+294**	**+558**	*n.d.*[c]

[a] Relative energy of the various conformations calculated at the B3LYP/6-31G(d) level; zero point energy corrections have been included. [b] For compounds **3** and **5**, conformations A, B, C, and D, the methoxy methyl is trans to the imine bond; for conformations Ac, Bc, Cc, and Dc, the methoxy methyl is cis. [c] Only the four C_2-symmetric conformations having the same orientation of the imine and aryl ring for both steroids were calculated; the Boltzmann-weighted sum of the calculated rotations was not determined, because there exist not fewer than 12 C_1-symmetric conformations of intermediate energy that were not calculated.

One finding was expected: having observed the isomerization of compound **3** by NMR, we were not surprised to see mutarotation as well. The specific rotation of **3** was observed to decay from $[\alpha]_D$ +763, 3 min after dissolution in $CHCl_3$, to $[\alpha]_D$ +581 at 3 hours, with little change thereafter. The observed half-life for this first-order process (see the Supporting Information) was 52.8 min at a nominal 23 °C, corresponding to $\Delta G^{\ddagger}$ = 22.3 kcal/mol, in good agreement with the NMR result.

The steroids imines described herein are conformationally complex, and it would be impractical to calculate the energies and specific rotations of *all* possible conformers at a reasonable level of theory. In order to simplify the problem, only the most highly preferred conformation of the steroid side chain, which is well known from analysis of hundreds of crystal structures,[9] was used as a starting point for the geometry optimizations. This conformation, which contains the maximum number of *anti* torsion angles, is also the low-energy conformation in gas phase calculations, and the conformation adopted by the molecule in Figure 1. Conformations resulting from rotations about the single and double C-N bonds in all compounds, as well as rotation about the aryl C-OMe bonds in compounds **3** and **5**, were evaluated by a systematic search of all possible rotamers. The results of these calculations are summarized in Table 1. All calculations, including calculations of optical rotation, were performed at the B3LYP/6-31G(d) level of theory using Gaussian03.[10] Analytical frequency calculations were performed for all conformations, and the relative energies shown in Table 1 contain zero point energy corrections. The specific rotations of the conformations were calculated by using the static polarizabilities. Frequency dependent polarizabilities are usually recommended for such work,[11] but an extensive evaluation of methods and basis sets for the calculation of the specific rotation of compound **1** indicated that the use of frequency dependent polarizabilities led to a gross overestimation of the specific rotation in this class of compounds (see the Supporting Information).

It is evident from the calculations (Table 1) that most conformations of compounds **3**, **5**, **6**, and **7** have large calculated specific rotations—up to 2300 for compound **6**. Unfortunately,

different conformations of the same molecule have calculated rotations of opposite sign, so the relative energy of the conformations determines the sign and magnitude of the observed specific rotations. The Boltzmann weighted sum of the calculated rotations has been provided in Table 1 for compounds **3**, **5**, and **6**. Only C_2-symmetric conformations of compound **7** were calculated (there are many C_1 conformations); thus, no weighted average was calculated.

At the B3LYP/6-31G(d) level, the most stable conformation for all of the compounds is "conformation D". For compound **3**, the two lowest energy conformations are the (*E*)-isomers D and Dc in Table 1, which differ only in the orientation of the *p*-methoxy group, and it is isomer Dc that is observed in both independent molecules of the crystal structure (see Figure 1). There are in total four (*E*)-isomers and four (*Z*)-isomers: in addition to the isomers D and Dc, the conformations A and Ac are the (*Z*)-isomers in which the aryl ring is tilted above ring A; conformations B and Bc are the (*E*)-isomers in which the aryl ring is tilted below ring A; and conformations C and Cc are the (*Z*)-isomers in which the aryl ring is tilted below ring A. However, all of these conformations lie within 1 kcal/mol of the ground state for compound **3**, so that each contributes significantly to the overall specific rotation at equilibrium. An analogous situation exists for compounds **5** and **6**. In this respect the steroid imines differ dramatically from the imines of camphorquinone (e.g. **1**), which generally possess only a single low energy conformation. It should be noted that the NMR spectrum of **3** shows only two subspectra because all four (*E*)-isomers interconvert rapidly at room temperature, as do all four (*Z*)-isomers; it is only the *E*/*Z* isomerization that is slow.

In order to limit the number of available conformations, we attempted to introduce a methyl group at C-2 of the steroid. The presence of the methyl would likely raise the energy of the (*E*)-isomers to a degree that they would no longer contribute significantly to the overall rotation. However, our alkylation reactions produced chiefly the 6-O-methylated compound **4**, rather than any C-methylated steroids. One imine of compound **4** was prepared (compound **5**), but it proved to have a somewhat lower specific rotation than the corresponding imine of **2** (compound **3**), although its ellipticity was rather greater. However, when detailed computational studies (which

were concomitant with the experimental work) were completed, it became clear that elimination of the (*E*)-isomers would still leave us with (*Z*)-isomer conformations of comparable energy but opposite rotation (essentially conformations A and C). For this reason, further attempts to alkylate at C-2 were abandoned.

The computational studies indicated that larger aromatic π-systems and the use of aromatic diamines for the synthesis of the arylimino steroids would at least give individual conformations with higher specific rotations than were possible with simple aniline derivatives (see Table 1). Furthermore, the camphorquinone derivative with the highest reported specific rotation ($[\alpha]_D$ 2875°) is the bisimine derived from bis(4-aminophenyl)amine.[12] It was for these reasons that we prepared the aminopyrene- and diaminonaphthalene-derived compounds **6** and **7**, but their observed rotations were no higher than for the simpler compounds. An additional complication for molecules with such large π-systems is that they have significant absorption at the sodium D line (589 nm). For **6** and **7**, the absorbance was tolerable, but the absorbance of moderately concentrated solutions of steroid diimines prepared from bis(4-aminophenyl)amine and bis(4-aminophenyl) ether was too great to permit the accurate measurement of their specific rotations (data not shown).

A pleasing aspect of the present work is the very good agreement of the experimental and calculated optical rotations, even though the calculations were performed at a relatively modest level of theory, B3LYP/6-31G(d). It was clear from calculations of the specific rotation of compound **1** (see the Supporting Information), that the results of the calculations show only modest basis set dependence, but a high variability with respect to the choice of method. B3LYP/6-31G(d) and B3PW91/6-31G(d) calculations employing static polarizabilities gave the best results for compound **1**, and so the former, very common method was chosen for the calculations of the steroid imines, which are chemically similar. In the case of the steroid imines, however, it is necessary to calculate accurately *both* the relative energies of the various conformations and their specific rotations, yet the experimental and calculated data for compounds **3** and **6** are in excellent agreement, and those for compound **5** are at least good.

Unfortunately, a complete evaluation of the conformations of compound **7** was beyond the reach of our present computational resources.

In conclusion, imines of cholest-4-ene-3,6-dione (**2**) are easily prepared (two steps from cholesterol) optically pure materials that exhibit specific rotations of several hundred degrees, but these values are not so high as the specific rotations of analogous imines prepared from the equally available camphorquinone. Individual conformations of the steroid imines are calculated to have very high specific rotations, but accessible conformations with both high positive and high negative rotations are present, so that the observed specific rotations are more modest. The agreement of the experimental and calculated specific rotations is very good, so that it may be possible to employ computational methods to design derivatives of related compounds with a more limited set of conformations and higher observed specific rotations.

Experimental

Cholest-4-ene-3,6-dione (2) was prepared by the method of Fieser.[7] Mp 121.5-123.5 °C (lit.[7] 122-123 °C); ^{1}H NMR ($CDCl_3$) δ 0.72 (s, 3 H), 0.861 (d, J = 7 Hz, 3 H), 0.866 (d, J = 7 Hz, 3 H), 0.92 (d, J = 7 Hz, 3 H), 1.16 (s, 3 H), 1.0-2.2 (methylene envelope, 22 H), 2.49 (m, 3 H), 2.68 (dd, J = 16 Hz, 4 Hz, 1 H), 6.17 (s, 1 H); ^{13}C NMR ($CDCl_3$) δ 11.9, 17.5, 18.6, 20.9, 22.6, 22.9, 23.8, 24.0, 28.00, 28.01, 34.0, 34.2, 35.5, 35.7, 36.0, 39.1, 39.4, 39.8, 42.5, 46.8, 50.9, 55.9, 56.5, 125.4, 161.1, 199.5, 202.3 (27 of 27 expected resonances).

3-(4-Methoxyphenylimino)cholest-4-en-6-one (3). Diketone **2** (199 mg, 0.500 mmol), anisidine (62 mg, 0.504 mmol), Na_2SO_4 (0.5 g), and EtOH (1 mL) were heated in a screw-capped tube on a boiling water bath for 1 h. The mixture was diluted with $CHCl_3$, the salt was filtered away, and the solution was concentrated to dryness. This material was fractionated by preparative TLC (solvent, 20:1 benzene-EtOAc). A bright yellow band with R_f = 0.43 was extracted from the silica with $CHCl_3$, and upon concentration gave compound **3** as an orange oil that crystallized upon standing (77.1 mg, 0.190 mmol, 38%). A portion of this material was recrystallized from EtOH to give bright yellow needles, mp 147.5-148.5 °C. At equilibrium in

solution, ^{1}H NMR analysis indicated that the imine **3** consisted of a roughly 3:2 mixture of isomers. ^{1}H NMR ($CDCl_3$) δ 0.71 (s, 3 H), 0.860 (d, J = 7 Hz, 3 H), 0.864 (d, J = 7 Hz, 3 H), 0.91 (d, J = 6 Hz, ~1.8 H), 0.93 (d, J = 6 Hz, ~1.2 H), 1.11 (s, 3 H), 1.0-2.1 (methylene envelope, 22 H), 2.33 (m, 1 H), 2.64 (m, 3 H), 3.79 (s, ~1.2 H), 3.80 (s, ~1.8 H), 6.46 (s, ~0.4 H), 6.70 (s, ~0.6 H), 6.73 (m, 2 H), 6.86 (m, 2 H); ^{13}C NMR ($CDCl_3$) δ 11.8, 18.2, 18.3, 18.6, 20.9, 21.0, 22.5, 22.8, 23.7, 23.9, 24.5, 28.0, 30.7, 33.7, 33.9, 35.2, 35.5, 35.6, 36.0, 39.0, 39.2, 39.4, 39.7, 42.4, 42.5, 46.4, 46.6, 50.5, 50.8, 55.4, 55.9, 56.5, 114.0, 114.1, 118.7, 121.3, 121.6, 130.5, 142.9, 143.4, 153.4, 154.5, 156.4, 156.5, 164.2, 166.0, 202.1, 203.2 (48 of 64 possible resonances for the cis and trans imine isomers); HRMS (ESI-TOF) *m/z* 504.3838 (M + H), calcd for $C_{34}H_{50}NO_2$ 504.3836; UV ($CHCl_3$) λ_{max} (log ε) 264 (4.0), 378 (3.4); $[\alpha]_D^{23}$ (*t* = 3 min) +763, $[\alpha]_D^{23}$ (*t* = 3 h) +581 (*c* 0.77, $CHCl_3$); CD ($CHCl_3$) λ_{max} ([θ]) 279 (–36,000), 385 (23,000).

6-Methoxycholesta-4,6-dien-3-one (4). Diisopropylamine (0.47 g, 4.6 mmol) was dissolved THF (10 mL) and cooled to 0 °C under argon. A solution of *n*-butyllithium (1.8 ml, 2.5 M in hexanes, 4.5 mmol) was added, and the resulting solution was stirred for 20 min, and then cooled to -78 °C. A solution of diketone **2** (1.20 g, 3.00 mmol) in THF (10 mL) was added, and after 30 min, iodomethane (0.37 mL, 6.0 mmol). The resulting yellow solution was stirred for 30 min, and then HMPA (1.8 mL) was added dropwise. After 2 h at -78 °C, the solution was left to warm to room temperature overnight. Ether and water were added, the separated organic layer was washed with saturated NH_4Cl (5 × 5 mL) and brine (5 × 10 mL), and it was dried over Na_2SO_4. This material was concentrated and fractionated by silica gel column chromatography (solvent, 8:1 hexanes-EtOAc) to yield compound **4** as pale yellow oil (0.81 g, 2.0 mmol, 66%). The site of methylation is evident from the fact that the two olefinic resonances in compound **4** are sharp singlets. This is to be expected for an isolated proton at C-4 (δ 6.23), and an olefinic proton at C-7 (δ 5.15) cannot couple strongly to the C-8 proton because of the unfavorable dihedral angle (~ 90°) formed by their respective C-H bonds. Had the product contained a 3-O-methyl group, the C-2 olefinic proton resonance of the resulting enol ether would have been coupled to the C-1 protons. ^{1}H NMR ($CDCl_3$) δ 0.75 (s, 3 H), 0.856 (d, J = 7 Hz, 3 H), 0.859 (d,

J = 7 Hz, 3 H), 0.91 (d, J = 6 Hz, 3 H), 1.10 (s, 3 H), 1.0-1.9 (methylene envelope, 20 H), 1.98 (ddd, J = 13, 5, 2 Hz, 1 H), 2.05 (dt, J = 16, 6 Hz, 1 H), 2.41 (dd, J = 18, 5 Hz, 1 H), 2.54 (ddd, J = 18, 14, 5 Hz, 1 H), 3.58 (s, 3 H), 5.15 (s, 1 H), 6.23 (s, 1 H); ^{13}C NMR ($CDCl_3$) δ 12.0, 16.4, 18.6, 20.6, 22.5, 22.8, 23.8, 23.9, 28.0, 28.1, 33.7, 34.2, 35.4, 35.7, 36.1, 36.4, 39.4, 39.5, 43.3, 51.0, 54.3, 54.7, 56.0, 109.1, 119.3, 149.9, 159.4, 199.9 (28 of 28 expected resonances); HRMS (ESI-TOF) *m/z* 413.3416 (M + H), calcd for $C_{28}H_{45}O_2$ 413.3414; UV ($CHCl_3$) λ_{max} (log ε) 304 (4.0); $[\alpha]_D^{24}$ +4 (*c* 2.85, $CHCl_3$).

3-(4-Methoxyphenylimino)-6-methoxycholesta-4,6-diene (5). Ketone **4** (201 mg, 0.490 mmol), anisidine (67 mg, 0.54 mmol), Na_2SO_4 (0.5 g), acetic acid (5 drops) and EtOH (5 mL) were mixed in a screw-capped tube and heated at 100 °C for 26 h. After cooling, the salt was filtered away, and the filtrate was concentrated to dryness. This material was fractionated by preparative TLC (solvent, 100:10:1 hexanes-EtOAc-Et_3N. A bright yellow band with R_f = 0.48 was extracted from the silica with $CHCl_3$, and concentration of this material gave imine **5** as yellow oil (52.1 mg, 0.101 mmol, 21%). This material resisted crystallization, but ^{1}H NMR analysis indicated that it was an 87:13 mixture of the imine **5** and the starting ketone **4**; the imine itself consisted of two isomers by NMR, present in a roughly 2:1 ratio. ^{1}H NMR ($CDCl_3$) δ 0.75 (s, 3 H), 0.858 (d, J = 7 Hz, 3 H), 0.862 (d, J = 7 Hz, 3 H), 0.90 (d, J = 6 Hz, ~2 H), 0.92 (d, J = 6 Hz, ~1 H), 1.05 (s, ~2 H), 1.08 (s, ~1 H), 1.0-2.8 (methylene envelope, 25 H), 3.45 (s, ~1 H, enol ether Me), 3.58 (s, ~ 2 H, enol ether Me), 3.74 (s, ~1 H, arom. OMe), 3.79 (s, ~2 H, arom. OMe), 4.96 (d, J = 1.5 Hz, ~0.3 H), 4.98 (d, J = 1.5 Hz, ~0.7 H), 6.74 (m, 2 H), 6.85 (m, 2 H); ^{13}C NMR ($CDCl_3$) δ 12.0, 16.6, 16.8, 18.6, 20.7, 20.8, 22.5, 22.8, 23.8, 23.9, 24.0, 24.6, 28.0, 28.1, 30.8, 34.1, 34.4, 35.2, 35.4, 35.7, 36.1, 36.5, 39.4, 39.6, 43.20, 43.23, 51.2, 51.3, 54.4, 54.56, 54.61, 54.65, 55.4, 55.7, 56.1, 105.2, 106.3, 111.4, 113.9, 114.7, 116.4, 121.4, 121.77, 121.81, 139.8, 144.3, 150.5, 150.6, 155.8, 165.4, 167.2 (51 of 66 possible resonances for the cis and trans imine isomers); HRMS (ESI-TOF) *m/z* 518.3993 (M + H), calcd for $C_{35}H_{52}NO_2$ 518.3993; UV ($CHCl_3$) λ_{max} (log ε) 302 (4.3), 352 (3.7); $[\alpha]_D^{24}$ +368 (*c* 0.19, $CHCl_3$) (this yields $[\alpha]_D^{24}$ +412 when corrected for the presence of 13% compound **4**); CD ($CHCl_3$) λ_{max} ([θ]) 344 (47,000).

3-(1-Pyrenylimino)cholest-4-en-6-one (6). Diketone **2** (202 mg, 0.51 mmol), 1-aminopyrene (113 mg, 0.52 mmol), Na_2SO_4 (0.5 g), and EtOH (2 mL) were mixed in a screw-capped tube and heated to 120 °C for 20 h. After cooling the mixture to room temperature, it was diluted with $CHCl_3$, the salt was filtered away, and the solution was concentrated to dryness. The resulting material was fractionated by preparative TLC (solvent, 7:1 hexanes-EtOAc). The red band with $R_f = 0.41$ was extracted from the silica with $CHCl_3$, and concentration gave crude imine **6** as a red-orange oil (74 mg, 0.12 mmol, 24%). A portion of this material was crystallized from ethanol to give orange imine **6**; mp 109-112 °C. ^{1}H NMR analysis indicated that this material was a 93:7 mixture of the imine **6** and the starting ketone **2**; the imine itself consisted of two isomers by NMR, present in a roughly 7:3 ratio. ^{1}H NMR ($CDCl_3$) δ 0.70 (s, 3 H), 0.867 (d, J = 7 Hz, 3 H), 0.872 (d, J = 7 Hz, 3 H), 0.90 (d, J = 6 Hz, ~2.1 H), 0.93 (d, J = 6 Hz, ~0.9 H), 1.13 (s, ~2.1 H), 1.17 (s, ~0.9 H), 1.0-3.0 (methylene envelope, 26 H), 6.24 (s, ~0.3 H), 6.98 (s, ~0.7 H), 7.33 (d, J = 8 Hz, ~0.3 H), 7.35 (d, J = 8 Hz, ~0.7 H), 7.99 (m, 5 H), 8.13 (m, 3 H); ^{13}C NMR ($CDCl_3$) δ 11.9, 18.2, 18.3, 18.6, 20.9, 21.0, 22.5, 22.8, 23.8, 24.0, 25.2, 28.0, 30.9, 33.8, 34.0, 35.2, 35.6, 36.0, 39.2, 39.3, 39.4, 39.8, 42.4, 42.5, 46.6, 50.6, 50.9, 55.9, 56.5, 56.6, 116.4, 117.6, 118.9, 120.7, 122.6, 122.8, 124.6, 124.7, 124.8, 124.9, 125.0, 125.1, 125.3, 125.9, 126.0, 126.1, 126.8, 127.0, 127.3, 127.9, 128.2, 129.9, 131.3, 131.6, 144.2, 145.2, 154.5, 155.5, 165.8, 167.8, 202.4, 202.8 (62 of 86 possible resonances for the cis and trans imine isomers); HRMS (ESI-TOF) *m/z* 598.4042 (M + H), calcd for $C_{43}H_{52}NO$ 598.4049; UV ($CHCl_3$) λ_{max} (log ε) 274 (4.4), 284 (4.4), 350 (4.2), 386 (3.7), 422 (3.6); $[\alpha]_D^{24}$ +513 (*c* 0.19, $CHCl_3$) (this yields $[\alpha]_D^{24}$ +552 when corrected for the presence of 7% compound **2**); CD ($CHCl_3$) λ_{max} ([θ]) 292 (–10,000), 338 (–11,000), 422 (13,000).

1,6-Bis[(6-ketocholest-4-en-3-ylidene)amino]naphthalene (7). Diketone **2** (404 mg, 1.02 mmol), 1,6-diaminonaphthalene (42 mg , 0.27 mmol), Na_2SO_4 (0.5 g), and EtOH (2 mL) were combined in a screw-capped tube and heated at 120 °C for 48 h. After cooling to room temperature, the mixture was diluted with $CHCl_3$, the salt was filtered away, and the solution was concentrated to dryness. This material was fractionated by preparative TLC (solvent, 5:2

hexanes-EtOAc). A yellow band with $R_f = 0.26$ was extracted from the silica with $CHCl_3$, and after concentration it was crystallized from EtOH to give yellow diimine **7** (27 mg, 0.029 mmol, 11%), mp 162-168 °C. ^{1}H NMR analysis showed two principal isomers, present in a roughly 7:3 ratio, and less than 3% of the starting diketone **2**. ^{1}H NMR ($CDCl_3$) δ 0.70 (s, 6 H), 0.857 (d, J = 7 Hz, 6 H), 0.861 (d, J = 7 Hz, 6 H), 0.90 (d, J = 6 Hz, ~4.2 H), 0.92 (d, J = 6 Hz, ~1.8 H), 1.11 (s, ~4.2 H), 1.14 (s, ~1.8 H), 1.0-2.9 (methylene envelope, 52 H), 6.31 (s, ~0.6 H), 6.70 (m, 2 H), 6.88 (s, ~1.4 H), 7.34 (m, 2 H), 7.44 (d, J = 8 Hz, ~1.4 H), 7.49 (d, J = 8 Hz, ~0.6 H); ^{13}C NMR ($CDCl_3$) δ 11.9, 18.2, 18.3, 18.6, 21.0, 22.5, 22.8, 23.7, 24.0, 24.8, 28.0, 30.7, 33.8, 34.0, 35.2, 35.6, 36.0, 39.2, 39.3, 39.4, 39.8, 42.5, 46.6, 50.6, 50.9, 55.9, 56.5, 56.6, 113.6, 114.9, 119.2, 119.6, 125.2, 125.3, 126.2, 127.2, 129.9, 146.2, 147.3, 154.3, 155.0, 165.1, 167.4, 202.4, 203.2 (45 resonances observed; a total of 130 resonances is possible for the three cis/trans isomers); MS (MALDI-TOF) *m/z* 918 (M^+, 100); HRMS (ESI-TOF) *m/z* 919.7076 (M + H), calcd for $C_{64}H_{91}N_2O_2$ 919.7081; UV ($CHCl_3$) λ_{max} (log ε) 266 (4.3), 308 (sh, 4.0), 404 (3.3); $[\alpha]_D^{24}$ +271 (*c* 0.23, $CHCl_3$); CD ($CHCl_3$) λ_{max} ([θ]) 281 (–4000), 314 (–15,000), 395 (15,000).

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Supporting Information: ^{1}H and ^{13}C NMR spectra of compounds **2**-**7**, kinetic data for the isomerization of **3**, circular dichroism spectra of compounds **3**, **5**, **6**, and **7**, calculated specific rotations of **1** and hexahelicene at various levels of theory, full reference 10, a crystallographic information file (CIF) for **3**, and an ASCII text file containing the atomic coordinates and energies of the calculated conformations of compounds **3**, **5**, **6**, and **7**. This information is available free of charge via the Internet at http://pubs.acs.org/.

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