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# Steroidal Lariat Ethers: A New Class of Macrocycles and the Crystal Structure of *N*-(Cholesteryloxycarbonyl)aza-15-crown-5

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Several examples of a new class of lariat ethers, those having steroidal side arms, are reported. These include the following carbon-pivot and nitrogen-pivot structures: 2-(3-dihydrocholesteryloxymethyl)-15-crown-5, mp 61-63 °C; *N*-(3-cholesteryloxycarbonylmethyl)aza-15-crown-5, mp 85–86 °C; *N*-(3-cholesteryloxycarbonylmethyl)aza-18-crown-6, mp 66–67 °C; *N*-(3-dihydrocholesteryloxycarbonylmethyl)aza-15-crown-5, mp 60–61 °C; *N*-(3-dihydrocholesteryloxycarbonylmethyl)aza-18-crown-6, mp 55–56 °C; *N*-(3-cholesteryloxycarbonyl)aza-15-crown-5, mp 96–98 °C; and *N*-(3-cholesteryloxycarbonyl)aza-18-crown-6, mp 82–84 °C. Alkali-metal cation binding by these structures is generally weak, since the macroring binding is not augmented by side arm donor group participation. The high lipophilicity of the side arm does not enhance the cation binding strength. The X-ray crystal structure of one of these novel lariat ethers, *N*-(cholesteryloxycarbonyl)aza-15-crown-5 has been determined. This is the first example of an uncomplexed, 15-membered crown ether compound containing only nitrogen and oxygen heteroatoms. The macroring structure has one N–C–C–O torsion angle anti; thus one methylene group is turned inward.

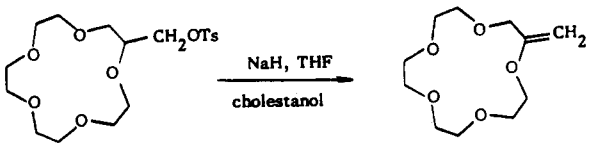
## Introduction

The interest in macrocyclic polyether compounds both as synthetic ionophores and in a variety of other applications continues to increase apace.[1] The understanding of these species has been aided considerably by the large number of cation binding,[2] dynamic,[3] and structure studies[4] which have been conducted. Our special interest is in the compounds we have named lariat ethers.[5] These are macrocyclic polyether compounds which have one or more side arms appended thereto. In most of the compounds we have studied thus far, the side arms bore donor groups that were conformationally accessible to a ring-bound cation. In this way, a three-dimensional array of donor groups was presented to the cation. We confirmed this arrangement both in solution and by several X-ray crystal structures.[6]

## Results and Discussion

One possible approach to the synthesis of a cation-conducting channel is to use lariat ethers having rigid side arms that could organize into a supramolecular system.

**Scheme I**




Our intention was to use the cholesteryl residue to form a liquid crystalline array in which the steroid residues were stacked. It was expected that the macrorings would then

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**Table I. Cation Binding Constants for Steroidal Lariat Ethers[a]**

| compd | ring size | pivot atom | linkage | side arm | $Na^+$ | $K^+$ |
|---|---|---|---|---|---|---|
| | 15 | | 15-crown-5 | | 3.29 | 3.43 |
| | 18 | | 18-crown-6 | | 4.34 | 6.09 |
| 3 | 15 | C | ether | dihydrocholesteryl | | |
| 4 | 15 | N | acetate | cholesteryl | 4.10 | 4.03 |
| 5 | 18 | N | acetate | cholesteryl | 4.56 | 5.75 |
| 6 | 15 | N | acetate | dihydrocholesteryl | 4.12 | 4.03 |
| 7 | 18 | N | acetate | dihydrocholesteryl | 4.58 | 5.78 |
| 8 | 15 | N | carbamate | cholesteryl | <1.5 | <1.5 |
| 9 | 18 | N | carbamate | cholesteryl | 2.07 | 1.78 |
| | 15 | N | | $CH_2CH_2OCH_3$ | 3.88 | 3.95 |
| | 18 | N | | $CH_2CH_2OCH_3$ | 4.33 | 6.07 |

[a] Binding constants determined in anhydrous methanol solution at 25 °C as described in ref 7 and 8.

be oriented as well and such a system might comprise a cation channel. We also felt that such compounds would be inherently interesting due to their very high lipophilicities.

**Syntheses.** When we began this work, we considered several different methods for attaching the cholesteryl units to the macrocycle. Our own experimental program presented two obvious variants in macrocycles as well: the carbon-[7] and nitrogen-pivot[8] lariat ether systems. From the mechanical point of view, a carbon-pivot, steroidal lariat ether offers a chemically stable species having a readily synthesized linkage.

Two obvious approaches to cholestanyl lariat ether **3** involve alkylation of the preformed macrocycle. In one case, the cholestanyl tosylate might serve as the alkylating agent; in the other, the crown tosylate would play this role. We anticipated that a secondary cyclohexyl tosylate derived from cholestanol (dihydrocholesterol) would eliminate rather than substitute. We attempted the second route but 2-[(tosyloxy)methyl]-15-crown-5 underwent elimination rather than substitution (Scheme I).

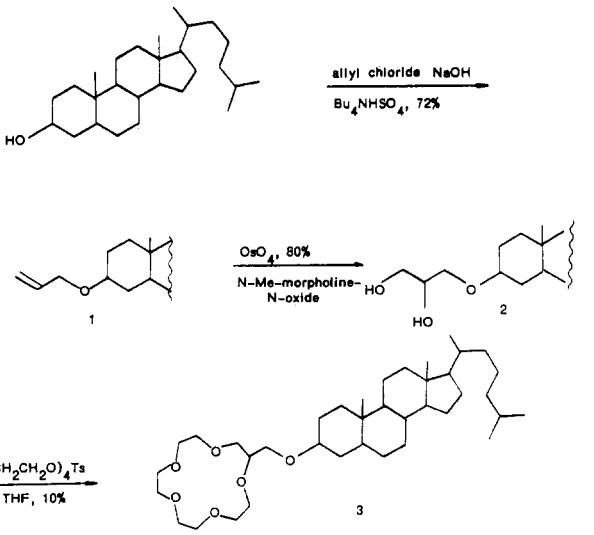
The synthesis of the carbon-pivot, cholestanyl lariat ether **3** was conducted as shown in Scheme II. Commercially available 3β-cholestanol (dihydrocholesterol) was O-allylated under phase-transfer catalytic conditions[9] to give the crystalline allyl cholestanyl ether, **1**, in 72% yield. Catalytic bishydroxylation using $OsO_4$ and *N*-methylmorpholine *N*-oxide,[7] afforded the crystalline diol **2** in 80% yield. Reaction of the dialkoxide derived from **2** (NaH, THF) with tetraethylene glycol ditosylate gave, after chromatography, cholestanyl lariat ether **3** in 10% yield as a glassy solid, mp 61–63 °C.

Azacrowns differ from the parent macrocycles in a variety of ways, most notably in basicity. Lariat ethers based on azacrown macrocycles in which the side arm is attached at the nitrogen atom are generally more flexible than their all-oxygen counterparts.[8]

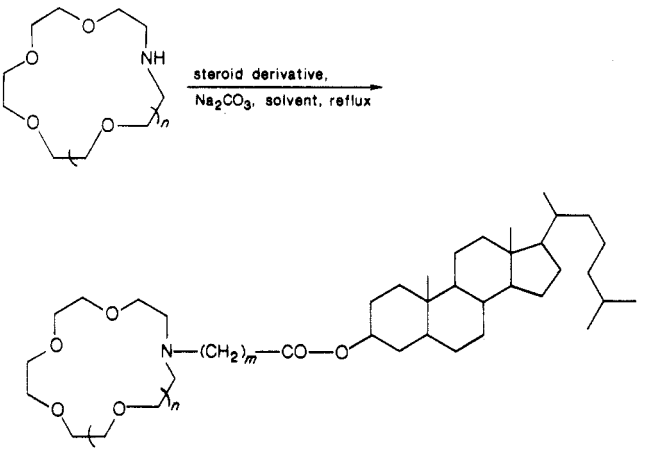
The direct analogue of **3** in the azacrown series would involve a $>N-CH_2-O$ linkage between macroring and side arm. Such a linkage is hydrolytically unstable, and the synthesis of this analogue was not attempted.

The corresponding N-substituted aza-15-crown-5 derivative was prepared in two steps from dihydrocholesterol. Chloroacetic acid was heated for a week with a slight excess of dihydrocholesterol in anhydrous benzene by using a Dean–Stark trap. Chromatography over silica gel G afforded the alkoxyacetic acid derivative as shiny, sheetlike crystals. Aza-15-crown-5, cholesteryl chloroacetate, and

**Scheme II**




**Scheme III**




**4**, $n=1$, $m=1$, unsaturated
**5**, $n=2$, $m=1$, unsaturated
**6**, $n=1$, $m=1$, saturated
**7**, $n=2$, $m=1$, saturated
**8**, $n=1$, $m=0$, unsaturated
**9**, $n=2$, $m=0$, unsaturated

$Na_2CO_3$ were heated in PrCN for 72 h. Cholesteryl crown **4** was obtained in 68% yield (mp 85–86 °C) after workup and chromatography (Scheme III). Cholesteryl lariat ether **5** was prepared similarly (63%, mp 66–67 °C).

The 15- (**6**) and 18-membered ring (**7**) analogues of **4** based on dihydrocholesterol were prepared similarly. Cholestanyl (4-aza-15-crown-5)acetate **6** was obtained as a white solid, mp 60–61 °C, in 67% yield. Likewise, **7** mp 53–54 °C, was obtained in 65% yield. The 15- (**8**) and 18-membered ring (**9**) derivatives having cholesterol linked to the azacrown by a carbamate residue were prepared in

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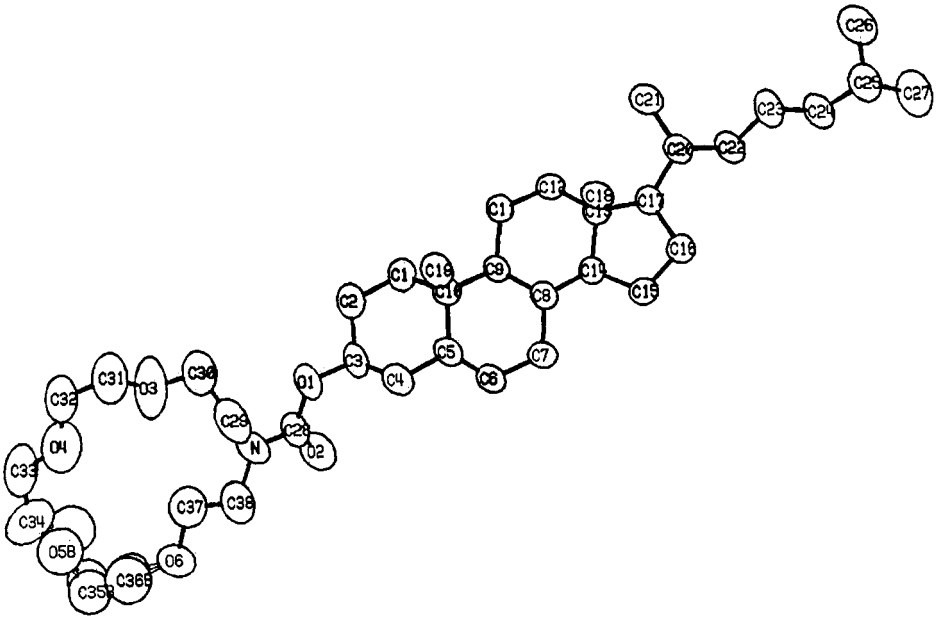


**Figure 1.** Structure of 8.

a single step from commercially available (Aldrich) cholesteryl chloroformate and the appropriate azacrown. Both the 15- (8) and 18-membered ring (9) derivatives proved crystalline and they were isolated in 34% and 52% yields, respectively. Recrystallization of 8 from anhydrous EtOH afforded crystals suitable for X-ray analysis.

**Cation Binding by Steroidal Lariat Ethers.** Cation binding constants (log $K_S$) in anhydrous methanol solution determined at 25 °C for the steroidal crown ethers prepared as part of this study are recorded in Table I. Several of these crown ethers are not true lariat ethers because they lack donor groups in the side arms. As a result, only the macroring itself is expected to provide cation binding sites. Previous studies of the equilibrium stability constants for the reaction ligand + $M^+ \rightleftharpoons$ complex have shown that 18-membered rings are generally stronger binders than analogous 15-membered ring compounds.[10] The magnitude of $K_S$ with such metals as $Na^+$ or $K^+$ is generally reduced in related systems when an oxygen donor is replaced by nitrogen. In compounds 8 and 9, not only has the poorer donor atom replaced oxygen, its donicity has been reduced by converting it from $sp^3$ to $sp^2$ hybridization.

**Structure of 8.** The most interesting feature of the structure is the ring conformation. Although several 15-membered ring structures have been reported in the past,[4] in all but two cases the macroring was complexed to a cation. The exceptions are Hanson's structure of benzo-15-crown-5[11] and 4,7-dithia-15-crown-5,[12] the structure of which was reported by Dalley and co-workers more than 10 years ago. Indeed, attempts at conformational analysis by Dale[13] and more recently by Wipff, Weiner, and Kollman[14] have ignored the 15-membered ring systems, probably in part because of the paucity of experimental data, even for the complexed species.

The structure of cholesteryl lariat 8 is shown in Figure 1. The structural features of the cholesteryl side arm are typical of known steroid systems.[15] In a search of the Cambridge Crystal Files, no carbamate esters were found, but even so, the distances, angles, and torsion angles of the ester linkage in 8 are similar to those reported for 21 carboxylate esters. The cholesteryl fragment of 6 is identical with those reported for other cholesteryl esters. Detailed comparisons of structural parameters are difficult because of the high $R$ factors usually associated with cholesteryl structures. In fact, the structure of 8 has a low $R$ factor when compared to previously reported cholesteryl ester structures.[15]

Uncomplexed 18-membered ring crown ether compounds containing only oxygen and nitrogen heteroatoms generally adopt the extended conformation first demonstrated by Dunitz for uncomplexed 18-crown-6.[16] The exceptions are diaza-18-crown-6[17] and triaza-18-crown-6, the latter being unpublished work from our laboratories. 4,7-Dithia-15-crown-5 appears to be dominated by the presence of the sulfur atoms. Both sulfur atoms turn outward and away from the ring. Because of this, the normal staggered arrangement for the $X-CH_2-CH_2-X$ linkages is found only between O4 and O5 in this compound. Indeed, the two sulfur atoms turn outward in the 12- and 15-membered ring dithiamacrocycles.

Structural details about the crown ring in the cholesteryl compound are less certain because of the disorder in atoms O5, C35, and C36. However, there are some features that are quite clear. Torsion angles about the C–C bonds in the crown are either $g^+$ or $g^-$, except C37–C38 which is $a$. The intrannular void of the ring is partly filled by C37, a methylene group. In general, the ring is more compressed in order to fill the cavity. The torsion angles about C31–O3, C32–O4, C33–O4, and C36–O6 are anti, but the torsion angles about C30–O3, C38–N, and N–C29 are anticlinal (116.0°, −119.0°, and −117.1°, respectively). The C–N

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Table II. Bond Distances (Å) and Bond Angles (deg) for *N*-(Cholesteryloxycarbonyl)aza-15-crown-5

| | | | |
|---|---|---|---|
| Bond Distances | | | |
| O1–C3 | 1.431 (4) | N–C38 | 1.479 (5) |
| O1–C28 | 1.351 (4) | C29–C30 | 1.489 (7) |
| O2–C28 | 1.216 (5) | C31–C32 | 1.433 (7) |
| O3–C30 | 1.407 (5) | C33–C34 | 1.431 (8) |
| O3–C31 | 1.234 (6) | C34–O5A | 1.31 (1) |
| O4–C32 | 1.293 (6) | C34–O5B | 1.19 (1) |
| O4–C33 | 1.334 (7) | C37–C38 | 1.439 (6) |
| O6–C37 | 1.414 (5) | C35A–O5A | 1.36 (2) |
| O6–C36A | 1.56 (2) | C35A–C36A | 1.26 (2) |
| O6–C36B | 1.60 (2) | C35B–O5B | 1.36 (2) |
| N–C28 | 1.330 (5) | C35B–C36B | 1.28 (2) |
| N–C29 | 1.461 (6) | | |
| Bond Angles | | | |
| C3–O1–C28 | 118.5 (3) | O3–C30–C29 | 111.4 (4) |
| C30–O3–C31 | 119.9 (5) | O3–C31–C32 | 118.0 (6) |
| C32–O4–C33 | 124.2 (5) | O4–C32–C31 | 117.2 (5) |
| C37–O6–C36A | 114.5 (5) | O4–C33–C34 | 115.7 (5) |
| C37–O6–C36B | 111.7 (6) | C33–C34–O5A | 118.3 (9) |
| C28–N–C29 | 120.9 (4) | C33–C34–O5B | 122.8 (10) |
| C28–N–C38 | 117.0 (4) | O6–C37–C38 | 109.0 (4) |
| C29–N–C38 | 119.4 (4) | N–C38–C37 | 113.8 (4) |
| O1–C3–C2 | 107.2 (3) | O5A–C35A–C36A | 95.5 (12) |
| O1–C3–C4 | 110.2 (4) | O5B–C35B–C36B | 93.7 (13) |
| O1–C28–O2 | 122.8 (4) | C34–O5A–C35A | 112.5 (11) |
| O1–C28–N | 110.4 (4) | C34–O5B–C35B | 139.2 (13) |
| O2–C28–N | 126.7 (4) | O6–C36A–C35A | 117.9 (10) |
| N–C29–C30 | 117.1 (5) | O6–C36B–C35B | 111.1 (13) |

torsion angles are expected to be different because the nitrogen atom is amidic. Selected bond angles and distances for the macroring are shown in Table II. Full details of bond distances and angles can be found in supplementary material.

In work conducted jointly with Okahara,[18] we found that $Na^+$ cation binding by 15-crown-5–$CH_2OCH_2CH_2OCH_3$ was considerably enhanced (nearly a power of 10) by the presence of a quaternary methyl group at the pivot atom (position 2 on the macroring). Although our first interpretation of this was based on steric hindrance, we eventually concluded that the difference was more likely due to a conformational effect. The sensitivity of conformation near the point of attachment in the present case encourages this view but cannot be conclusive since the C- and N-pivot systems are not directly comparable.

## Summary

Synthetic access to a new class of steroidal lariat ethers is presented. These include carbon- and nitrogen-pivot systems and both 15- and 18-membered ring systems. These compounds are not strong cation binders despite their high lipophilicity. The X-ray crystal structure of *N*-(cholesteryloxycarbonyl)aza-15-crown-5 is reported and shows the inward-turned ring methylene, characteristic of uncomplexed 18-membered ring crown ethers.

## Experimental Section

Melting points (Thomas-Hoover apparatus, open capillaries) are uncorrected. Infrared (IR) spectra were recorded on a Perkin-Elmer 281 spectrophotometer as neat samples unless otherwise noted. Spectral bands are reported in $cm^{-1}$ and calibrated against the 1601-$cm^{-1}$ band of polystyrene. Proton nuclear magnetic resonance ($^1H$ NMR) spectra were recorded at 60 MHz as ca. 15 wt % solutions in $CDCl_3$ unless otherwise specified. Chemical shifts are reported in parts per million ($\delta$) downfield from internal $Me_4Si$ and are reported in the order: chemical shift, spin multiplicity (br = broad; s = singlet; d = doublet; t = triplet; q = quartet; m = multiplet), and integration. Combustion analyses (C, H, N) were performed by Atlantic Microlabs, Atlanta, GA.

All reagents were the best grade commercially available and were used without further purification unless otherwise specified. Cholesterol, dihydrocholesterol (cholestanol), and cholesteryl chloroformate were purchased from Aldrich Chemical Company. All solvents were distilled prior to use and tetrahydrofuran (THF) was distilled from $LiAlH_4$ or Na–benzophenone. Benzene and dioxane were dried by distillation from Na–benzophenone under a dry $N_2$ atmosphere immediately before use. *N*,*N*-Dimethylformamide (DMF) was dried by distillation from CaO prior to use. Oven temperatures are given for bulb-to-bulb distillations conducted in a Kugelrohr apparatus. Preparative chromatography columns were packed with MCB activated $Al_2O_3$ (80–325 mesh, chromatographic grade, AX-611) or Fluka silica gel 60 (70–230 mesh, chromatographic grade). Precoated sheets (aluminum oxide 60 F-254 neutral-Type E or silica gel 60 F-254) 0.2 mm thick were used for TLC analyses.

***N*-Benzylaza-15-crown-5.** Benzyl chloride (557.0 g, 4.4 mol) was allowed to react with diethanolamine (420.0 g, 4.0 mol) to afford *N*-benzyldiethanolamine after vacuum distillation (609 g, 78%): bp 143–145 °C (0.1 torr). *N*-Benzylaza-15-crown-5 was prepared by cyclization of *N*-benzyldiethanolamine (195 g, 1.0 mol) with triethylene glycol ditosylate (458.0 g, 1.0 mol) as described in ref 8b. The crude mixture was chromatographed ($Al_2O_3$, hexanes) and distilled [Kugelrohr, 125 °C (0.1 torr)] to give the macrocyclic polyether (142.0 g, 46%) as a colorless oil.

**Aza-15-crown-5** was prepared by hydrogenolysis of *N*-benzylaza-15-crown-5, as described previously. The title compound [6.5 g, 98%; bp 76 °C (0.05 torr)] was isolated as a colorless oil, which solidified to a soft, white hygroscopic solid (mp 30–32 °C).

***N*-Benzylaza-18-crown-6** was prepared as described above for the 15-membered ring analogue, except that cyclization was effected with tetraethylene glycol ditosylate (502.0 g, 1.0 mol). The crude mixture was chromatographed ($Al_2O_3$, hexanes) and distilled [Kugelrohr, 130 °C (0.05 torr)] to give *N*-benzylaza-18-crown-6 (140 g, 40%) as a colorless oil.[8b]

**Aza-18-crown-6** was obtained by hydrogenolysis of *N*-benzylaza-18-crown-6 as described above [10.0 g, 98%, mp 49–51 °C, bp 125 °C (0.25 torr)].

**3β-Cholestanyl Allyl Ether (1).** A solution of 3β-cholestanol (15.0 g, 38.6 mmol), allyl chloride (118.5 g, 1.55 mol), 50% aqueous NaOH (15.0 g, 38.6 mmol), and tetra-*n*-butylammonium bisulfate (TBAB) (3.0 g, 8.9 mmol) was heated at reflux temperature for 13 days. The mixture was cooled to room temperature, water (150 mL) and ether (50 mL) were added to dissolve the salts, and the phases were separated. The aqueous phase was extracted with $Et_2O$ (3 × 100 mL). The organic extracts were combined and evaporated in vacuo. Chromatography on silica (200 g, 15–25% $CH_2Cl_2$ in hexane) gave **1** (10.1 g, 61%) as a white crystalline solid, mp 68–69 °C: $^1H$ NMR ($CDCl_3$) 0.7–2.1 (m, 47 H, steroid), 3.2–3.3 (m, br, 1 H, CHO), 4.0 (d, 2 H, $CH_2$ allyl), 5.02–5.24 (m, 2 H, C=$CH_2$), 5.6–6.2 (m, 1 H, HC=C); IR (mineral oil) 2920 (s), 2840 (s), 1450, 1360, 1090, 915 $cm^{-1}$. Anal. Calcd for $C_{30}H_{52}O$: C, 84.04; H, 12.22. Found: C, 83.91; H, 12.15.

**3-(Cholestanyloxy)-1,2-propanediol (2).** Compound **1** (5.0 g, 11.6 mmol), *N*-methylmorpholine *N*-oxide (1.75 g, 13.0 mmol), and $OsO_4$ (5 mg, 0.02 mmol) in a solution of 10:3:1 *tert*-butyl alcohol/THF/water (700 mL) was heated to reflux temperature for 3 days. The mixture was cooled to room temperature and concentrated in vacuo. Recrystallization (MeOH) afforded **2** (4.3 g, 80%) as a white crystalline solid (mp 102–104 °C): $^1H$ NMR ($CDCl_3$) 0.7–2.1 (m, 47 H, steroid), 2.6–2.7 (m, 2 H, OH), 3.2–3.3 (m, br, 1 H, CHO), 3.5–3.9 (m, 5 H, $CH_2CHCH_2O$) [when $D_2O$ was added, the multiplet at $\delta$ 2.6–2.7 disappeared]; IR (mineral oil) 3400 (s), 2910 (s), 2840 (s), 1450, 1360, 1100 $cm^{-1}$. Anal. Calcd for $C_{30}H_{54}O_3$: C, 77.87; H, 11.76. Found: C, 77.62; H, 11.70.

**(Cholestanyloxymethyl)-15-crown-5 3.** Sodium hydride (50% dispersion in mineral oil, 940 mg, 39.0 mmol) was washed with hexanes (3 × 100 mL) and suspended in THF (400 mL), and the mixture was brought to reflux. A mixture of compound **2** (9.0 g, 19.5 mmol) and tetraethylene glycol ditosylate (9.8 g, 19.5 mmol) in THF (175 mL) was added slowly during 1 h. The mixture was cooled to room temperature, filtered, and evaporated in vacuo.

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Table III. Coordinates for Sterodial Lariat: Compound 8[a]

| Atom | x | y | z | Atom | x | y | z |
|---|---|---|---|---|---|---|---|
| O1 | 0.6352(2) | 1 | 0.1934(2) | C17 | 1.3112(3) | 0.9578(6) | 0.5546(2) |
| O2 | 0.5122(3) | 0.8654(6) | 0.2580(2) | C18 | 1.2649(4) | 1.1755(6) | 0.4658(3) |
| O3 | 0.4700(4) | 1.0561(8) | -0.0219(2) | C19 | 0.9700(4) | 1.1821(7) | 0.2929(3) |
| O4 | 0.2749(4) | 1.0304(12) | -0.1043(3) | C20 | 1.4335(3) | 0.9940(6) | 0.5581(3) |
| O6 | 0.1722(3) | 0.9317(8) | 0.1313(2) | C21 | 1.4909(4) | 0.9459(8) | 0.4840(3) |
| O5A * | 0.1203(8) | 0.8592(15) | -0.0336(6) | C22 | 1.4904(4) | 0.9299(7) | 0.6329(3) |
| O5B * | 0.0795(8) | 0.9907(13) | -0.0366(5) | C23 | 1.5963(4) | 1.0017(7) | 0.6577(3) |
| N | 0.4614(3) | 1.0270(6) | 0.1597(2) | C24 | 1.6463(4) | 0.9394(9) | 0.7343(3) |
| C1 | 0.9232(4) | 0.9163(7) | 0.2576(3) | C25 | 1.7397(4) | 1.0251(10) | 0.7730(3) |
| C2 | 0.8235(4) | 0.9472(7) | 0.2018(3) | C26 | 1.8329(5) | 1.0403(11) | 0.7235(4) |
| C3 | 0.7216(4) | 0.9561(7) | 0.2479(3) | C27 | 1.7741(5) | 0.9545(14) | 0.8538(4) |
| C4 | 0.7318(4) | 1.0632(7) | 0.3150(3) | C28 | 0.5326(4) | 0.9580(8) | 0.2084(3) |
| C5 | 0.8335(3) | 1.0434(6) | 0.3687(3) | C29 | 0.4953(5) | 1.1502(8) | 0.1102(4) |
| C6 | 0.8276(3) | 1.0391(6) | 0.4462(3) | C30 | 0.5469(5) | 1.1120(10) | 0.0345(3) |
| C7 | 0.9228(3) | 1.0257(6) | 0.5038(2) | C31 | 0.4501(6) | 1.1246(11) | -0.0841(4) |
| C8 | 1.0317(3) | 1.0514(6) | 0.4645(2) | C32 | 0.3639(5) | 1.0714(11) | -0.1363(3) |
| C9 | 1.0316(3) | 0.9719(6) | 0.3848(2) | C33 | 0.1872(7) | 0.9800(16) | -0.1450(4) |
| C10 | 0.9401(3) | 1.0289(6) | 0.3266(2) | C34 | 0.0985(7) | 0.9347(16) | -0.0984(4) |
| C11 | 1.1444(3) | 0.9669(7) | 0.3497(2) | C35A * | 0.0444(10) | 0.8786(18) | 0.0216(7) |
| C12 | 1.2367(3) | 0.9196(6) | 0.4081(2) | C35B * | 0.0304(11) | 0.9567(20) | 0.0316(8) |
| C13 | 1.2382(3) | 1.0143(6) | 0.4837(2) | C36A * | 0.1011(9) | 0.8239(14) | 0.0784(6) |
| C14 | 1.1255(3) | 0.9978(6) | 0.5181(2) | C36B * | 0.0961(12) | 1.0346(21) | 0.0748(8) |
| C15 | 1.1384(3) | 1.0649(7) | 0.6004(2) | C37 | 0.2827(5) | 0.9396(12) | 0.1112(4) |
| C16 | 1.2543(3) | 1.0182(7) | 0.6281(3) | C38 | 0.3447(5) | 1.0083(10) | 0.1754(3) |

[a] Atoms marked with * have population = $^1/_2$.

Column chromatography (silica gel, 0–10% acetone/hexanes) afforded **3** (1.2 g, 10%) as a slightly yellow, glass solid (mp 61–63 °C): $^1$H NMR ($CDCl_3$) 0.7–2.1 (m, 47 H, steroid), 3.4–3.7 (m, 22 H, $CH_2O$ and HCO); IR (neat) 2920 (s), 2860 (s), 1470, 1380, 1300, 1120 cm$^{-1}$. Anal. Calcd for $C_{38}H_{68}O_6$: C, 73.50; H, 11.04. Found: C, 73.31; H, 11.31. $[\alpha]^{25}_D$ +8.53° (*c* 1.7, $CHCl_3$).

**Cholesteryl Chloroacetate.** A solution of cholesterol (1.93 g, 5 mmol) and triethylamine (0.51 g, 5 mmol) in benzene (25 mL) was added dropwise to an 8–10 °C solution of chloroacetyl chloride (0.57 g, 5 mmol) in benzene (20 mL). The solution was heated under reflux at 80 °C for 24 h, cooled to room temperature, and worked up. Recrystallization (absolute EtOH) afforded the title compound (1.53 g, 66%) as a white solid (mp 160–161 °C).

**Cholesteryl (4-Aza-15-crown-5)acetate 4.** Cholesteryl chloroacetate (0.50 g, 1.1 mmol), aza-15-crown-5 (0.24 g, 1.1 mmol), and $Na_2CO_3$ (0.13 g, 1.2 mmol) were heated at reflux (115 °C) in butyronitrile (40 mL) for 72 h. The mixture was cooled, filtered, and concentrated in vacuo. Column chromatography (silica gel, 5% 2-propanol/hexanes) afforded pure **4** (0.48 g, 68%) as a white solid (mp 85–86 °C): $^1$H NMR ($CDCl_3$) 0.58–2.65 (m, 43 H, steroid), 2.93 (t, 4 H, $CH_2NCH_2$), 3.40–3.93 (m, 18 H, crown and $NCH_2CO$), 4.36–4.86 (br s, 1 H, >CHO), 5.30 (br s, 1 H, C=CH). IR ($CCl_4$) 2990 (s), 2900 (s), 1740 (w), 1190 (s) cm$^{-1}$; $[\alpha]^{25}_D$ -23.85° (*c* 2, $CHCl_3$). Anal. Calcd for $C_{39}H_{67}NO_6$: C, 72.49; H, 10.46. Found: C, 72.24; H, 10.54.

**Cholesteryl (4-Aza-18-crown-6)acetate 5.** Cholesteryl chloroacetate (0.69 g, 1.5 mmol), aza-18-crown-6 (0.40 g, 1.5 mmol), and $Na_2CO_3$ (0.19 g, 1.8 mmol) in butyronitrile (45 mL) were set to reflux (115 °C) during 60 h. The reaction mixture was cooled to ambient temperature, filtered, and concentrated in vacuo. Column chromatography (silica gel, 2% MeOH/$CH_2Cl_2$) afforded **5** (0.65 g, 63%) as a waxy, slightly yellow solid (mp 66–67 °C): $^1$H NMR 0.57–2.57 (m, 43 H, steroid), 2.97 (t, 4 H, $NCH_2$), 3.37–3.87 (br s, 22 H, crown and $NCH_2CO$), 4.27–4.97 (s, br, 1 H, >CHO), 5.27–5.47 (br s, 1 H, CH=C); IR ($CCl_4$) 2980 (s), 2900 (s), 1740 (s), 1130 (s) cm$^{-1}$; $[\alpha]^{25}$D -20.6° (*c* 2, $CHCl_3$). Anal. Calcd for $C_{41}H_{71}NO_6$: C, 73.07; H, 10.61. Found, C, 73.37; H, 10.91.

**Dihydrocholesteryl Chloroacetate.** A solution of dihydrocholesterol (1.94 g, 5 mmol) and triethylamine (0.51 g, 5 mmol) in benzene (25 mL) was added dropwise to an 8–10 °C solution of chloroacetyl chloride (0.57 g, 5 mmol)e in benzene (20 mL). The solution was heated at reflux (80 °C) for 24 h, cooled to room temperature, and filtered. The solution was concentrated in vacuo, and the residue was dissolved in $CH_2Cl_2$ (50 mL) and consecutively washed with 3 N HCl (4 × 25 mL), a 5% $Na_2CO_3$ solution (2 × 25 mL), and water (25 mL). The organic phase was dried ($Na_2SO_4$) and concentrated in vacuo. Recrystallization (absolute EtOH) afforded cholesteryl chloroacetate (1.5 g, 65%) as a white solid (mp 180–181 °C): $^1$H NMR ($CDCl_3$) 0.66–2.16 (m, 46 H, steroid), 3.97 (s, 2 H, $ClCH_2CO_2$), 4.43–4.97 (s, br, 1 H, CHO). IR ($CCl_4$) 2985(s), 1750(s), 1185(s) cm$^{-1}$. This compound was used directly in the next step.

**Cholestanyl (4-Aza-15-crown-5)acetate 6.** Dihydrocholesteryl chloroacetate (0.50 g, 1.1 mmol), aza-15-crown-5 (0.24 g, 1.1 mmol), and $Na_2CO_3$ (0.13 g, 1.2 mmol) were heated in butyronitrile (40 mL) at reflux (115 °C) for 72 h. The mixture was cooled to room temperature, filtered, and concentrated in vacuo. Column chromatography (silica gel, 5% 2-propanol/hexanes) afforded pure **6** (0.48, 67%) as a white solid (mp 60–61 °C): $^1$H NMR ($CDCl_3$) 0.47–2.23 (m, 46 H, steroid), 2.92 (t, 4 H, $CH_2CH_2$) 3.33–3.83 (m, 18 H, crown and $NCH_2CO_2$), 4.27–4.96 (br s, 1 H, CHO); IR ($CCl_4$) 2930 (s), 2900 (s), 1740 (w), 1190 (s) cm$^{-1}$; $[\alpha]^{25}_D$ +12.10° (*c* 2, $CHCl_3$). Anal. Calcd for $C_{39}H_{69}NO_6$: C, 72.27; H, 10.74. Found: C, 72.09; H, 10.74%.

**Cholestanyl (4-Aza-18-crown-6)acetate 7.** The procedure described above for the synthesis of **5** was followed, and the title compound was obtained (0.18 g, 65%) as a waxy, slightly yellow solid (mp 55–56 °C): $^1$H NMR 0.47–1.97 (m, 46 H, steroid), 2.93 (t, 4 H, $NCH_2$), 3.37–3.83 (m, 22 H, crown and $NCH_2CO$), 4.30–4.87 (br s, 1 H, >CHO); IR ($CCl_4$) 2940 (s), 2900 (s), 1740 (s), 1150 (s) cm$^{-1}$; $[\alpha]^{25}_D$ +9.4° (*c* 2, $CHCl_3$).

***N*-(Cholesteryloxycarbonyl)aza-15-crown-5 8.** Aza-15-crown-5 (2.0 g, 9.0 mmol) and $Et_3N$ (1.4 g, 14.0 mmol) in DMF (50 mL) were heated to ca. 90 °C. Cholesteryl chloroformate (3.6 g, 8.0 mmol) was added, and the temperature was maintained at ca. 90 °C for 48 h. The mixture was cooled to room temperature, filtered, and concentrated in vacuo. Column chromatography (silica gel, 5% EtOAc/$CHCl_3$) followed by recrystallization (absolute EtOH) afforded pure **8** (2.0 g, 34%) as a white crystalline solid (mp 96–98 °C): $^1$H NMR ($CDCl_3$) 1.5 (m, 44 H, steroid), 3.63 (m, 20 H, $OCH_2CH_2O$ and $CH_2CH_2$), 5.30 (dd, 1 H, C=CH); IR (KBr) 2940, 1705, 1230, 1160, 1130 cm$^{-1}$. Anal. Calcd for $C_{38}H_{65}NO_6$: C, 72.62; H, 10.22; N, 2.19. Found: C, 72.90; H, 10.50; N, 2.00. Crystals for X-ray analysis: **8** (1.0 g) was recrystallized from absolute EtOH (20 mL) to afford needles suitable for analysis.

***N*-(Cholesteryloxycarbonyl)aza-18-crown-6 9.** Aza-18-crown-6 (2.0 g, 8.0 mmol), $Et_3N$ (1.4 g, 14.0 mmol), and DMF (50

mL) were heated to ca. 90 °C. Cholesteryl chloroformate (3.6 g, 8.0 mmol) was added, and the temperature was maintained at ca. 90 °C for 48 h. The mixture was cooled to room temperature, filtered, and concentrated in vacuo. Column chromatography (silica gel, 5% EtOAc/$CHCl_3$) followed by recrystallization (absolute EtOH) afforded pure **9** (2.75 g, 52%) of a white solid (mp 82–84 °C): $^1$H NMR ($CDCl_3$) 1.50 (m, 44 H, steroid), 3.63 (m, 24 H, $OCH_2CH_2O$ and $CH_2NCH_2$), 5.30 (dd, 1 H, C=CH); IR (KBr) 2940, 1705, 1470, 1380, 1160, 1130 $cm^{-1}$. Anal. Calcd for $C_{40}H_{69}NO_7$: C, 71.09; H, 10.29; N, 2.07. Found: C, 70.97; H, 10.20; N, 2.14.

**X-ray Experimental.** The structure of **8** was solved with data collected with Cu K$\alpha$ radiation on a Nicolet P3/F diffractometer, by employing the SHELXTL system.[19] The orientation of the steroid ring system was determined by using the direct methods program SOLV, and its position relative to the symmetry axis was determined by translational search. Refinement was carried out with data collected on an Enraf-Nonius CAD4 diffractometer with Cu K$\alpha$ radiation. Crystal data: $C_{38}H_{65}NO_6$, MW 631.9, monoclinic space group $P2_1$, $Z = 2$, $a = 12.293$ (2) Å, $b = 9.027$ (4) Å, $c = 16.858$ (2) Å, $\beta = 92.34$ (1)°, $V = 1869.2$ (14) Å$^3$, $D_c = 1.123$ g $cm^{-3}$, $\lambda =$ 1.54184 Å, $\mu = 5.53$ $cm^{-1}$, $T = 24$ °C. Data were collected by $\omega$–$2\theta$ scans of speeds varying 0.83–4.0 deg $min^{-1}$. One quadrant of data within $2° < \theta < 75°$ yielded 4100 unique reflections, of which 2676 were considered observed, having $I > 1\sigma(I)$. Data reduction included corrections for background, Lorentz, polarization, and absorption by $\mu$ scans. The absolute configuration was assumed to correspond to that determined for other cholestanes.[15] Refinement was carried out by full-matrix least squares based on $F$ with weights $w = \sigma^{-2}(F_o)$. Except for the disordered region, non-hydrogen atoms were refined anisotropically, and H atoms were placed in calculated positions. The three disordered atoms were assigned population = $^1/_2$ in six sites and refined isotropically, with H atoms ignored. Final $R = 0.074$ for 402 variables, with maximum electron density 0.22 e Å$^3$. Coordinates are listed in Table III; coordinates for hydrogen atoms and anisotropic thermal parameters are given in the supplementary material.

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**Supplementary Material Available:** Anisotropic thermal parameters and coordinates for hydrogen atoms in $C_{38}H_{65}NO_6$ (3 pages). Ordering information is given on any current masthead page.

# 2,4-Cyclohexadien-1-ones in Organic Synthesis. Further Studies of Molecular Rearrangements Occurring from Products of Intramolecular Azide–Olefin Cycloadditions

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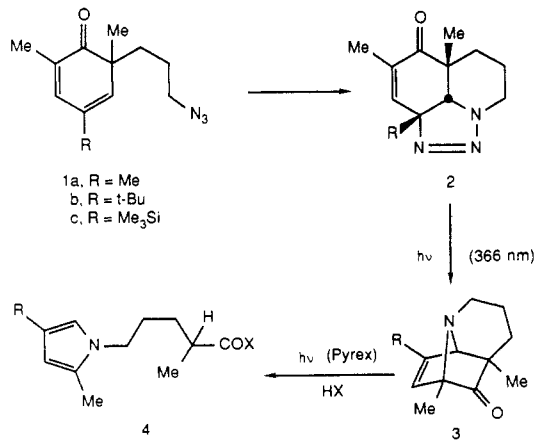
Thermolyses of 6-(3-azidopropyl)-2,4-cyclohexadien-1-ones **7a** and **7b** provide triazolines **8a** and **8b**, respectively. Photolysis of **8b** (366 nm) in methanol solution gives 2-azatricyclo[4.4.0.0$^{2,8}$]dec-9-en-7-one **9**, but photolysis of **8a** gives the pyrrole malonic ester **10a**. The inability to isolate the corresponding azatricycle **11** is explained by the operation of a retro-Mannich reaction of **11** to give zwitterion **12**, from which fragmentation occurs to give pyrrole ketene **13**. Reaction of **13** with methanol generates pyrrole malonic ester **10a**. Photolysis of **7a** (366 nm) in methanol solution gives azido diene **15**; thermolysis of **15** at 80 °C gives a mixture of diastereomeric vinylaziridines **16**. Acid-catalyzed rearrangement of **16** gives the butadiene carboxylic ester **17**, while thermolysis of **16** at 80–140 °C provides vinylogous urethane **20**. The rearrangement of **16** to **20** is suggested to occur by zwitterionization of **16** to give carbonyl-stabilized azomethine ylide **19**, followed by hydrogen atom rearrangement. Cycloadduct **21** is obtained on thermolysis of **16** in the presence of excess dimethyl acetylenedicarboxylate (DMAD). Vinylaziridine **23** (obtained from 2,4-cyclohexadienone **7b** via azido diene **22**) is stable to *p*-toluenesulfonic acid in THF at room temperature and attempted thermolysis at 140 °C.

Triazolines **2a–c** formed by intramolecular cycloaddition of 6-(3-azidopropyl)-2,4-cyclohexadien-1-ones **1a–c** photorearrange to 2-azatricyclo[4.4.0.0$^{2,8}$]dec-9-en-7-ones **3a–c** (Scheme I).[1] Azatricycles **3a–c** are photostable at 366 nm but undergo efficient photoconversion to pyrrole carboxylic acid derivatives **4a–c** on irradiation through Pyrex glassware. The fragmentation of **3a–c** presumably occurs by a photoinitiated retro-Diels–Alder reaction to give intermediate pyrrole ketenes (not shown), followed by addition of solvent (HX) to the ketene.

The sequence of reactions **1** → **2** → **3** provides a method for accomplishing the synthetic equivalence of an intramolecular cycloaddition between a diene and a nitrene. However, a limiting feature of the methodology is that the preparation of **1a–c** is based on C-alkylation of phenolic precursors. This procedure for construction of 2,4-cyclohexadienones requires the utilization of symmetrical 2,6-disubstituted phenols and only the most reactive alkylation

**Scheme I**

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