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# Cobalt(I)-Catalyzed [6π + 2π] Cycloaddition of 1,2-Dienes and 1,3-Diynes to *N*-Carbocholesteroxyazepine in the Synthesis of Previously Undescribed Heterofunctional 9-Azabicyclo[4.2.1]nonadi(tri)enes

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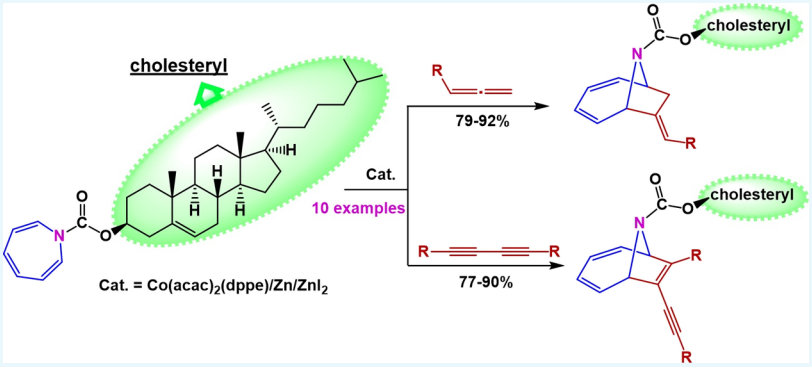


**ABSTRACT:** Promising heterofunctional (*E*)-9-azabicyclo[4.2.1]nona-2,4-dienes (79−92%) and 9-azabicyclo[4.2.1]nona-2,4,7-trienes (77−90%) containing a cholesterol fragment in the structure have been synthesized for the first time through the [6π + 2π] cycloaddition reaction of terminal 1,2-dienes and symmetric 1,3-diynes with *N*-carbocholesteroxyazepine under the action of the $Co(acac)_2(dppe)/Zn/ZnI_2$ three-component catalytic system.

## INTRODUCTION

Earlier,[1] we have first presented an efficient one-pot method for the synthesis of substituted 9-azabicyclo[4.2.1]nona-2,4,7-trienes and 9-azabicyclo[4.2.1]nona-2,4-dienes based on cobalt(I)-catalyzed cycloaddition of the simplest *N*-carboalkoxyazepines to alkynes, 1,3-diynes, and 1,2-dienes. It is noteworthy that research work in the field of synthesis of new derivatives of 9-azabicyclo[4.2.1]nonanes is of high practical relevance, since the 9-azabicyclo[4.2.1]nonane backbone is a key structural element of a number of important alkaloids (anatoxin-a,[2] pinnamine,[3] and bis-homoepibatidine[4]) with diverse biological activity (Figure 1).

In particular, these alkaloids and their synthetic analogues (e.g., UB-165[5]) exhibit pronounced activity toward the *n*-cholinergic receptor. Therefore, they are extremely demanded in modern studies upon creating advanced drugs for the treatment of serious mental illness, associated with imbalance of neurotransmitters.[2l,l,5b−h] Thus, the development of efficient methods for the design of new biologically active molecules with a 9-azabicyclo[4.2.1]nonane backbone, in our opinion, might considerably enrich the arsenal of potential precursor compounds of innovative drugs for the treatment of socially significant human diseases.

Meanwhile, the synthesis of 9-azabicyclo[4.2.1]nonanes applying metal-promoted and metal-catalyzed cycloaddition reactions of N-substituted 1*H*-azepines remains almost unexplored field. So far, there are only a few reported studies on the photochemical cyclocodimerization of tricarbonyl($\eta^6$-*N*-carboalkoxyazepine)chromium(0)[6] and tricarbonyl($\eta^6$-*N*-cyanoazepine)chromium(0)[7] with alkenes, 1,3-dienes, and alkynes. Moreover, before our studies started,[1,8] there had been no information available on the catalytic transformations of N-substituted azepines, except for two reactions of Cr(0)-catalyzed cycloaddition of *N*-carbomethoxyazepine[6d] and *N*-carbethoxyazepine[9] to ethyl acrylate (Scheme 1).

In the development of advanced research in the chemistry of 9-azabicyclo[4.2.1]nonanes, we have recently[10] synthesized for the first time *N*-carbocholesteroxyazepine in order to obtain on its basis novel 9-azabicyclo[4.2.1]nonadi(tri)enes containing a

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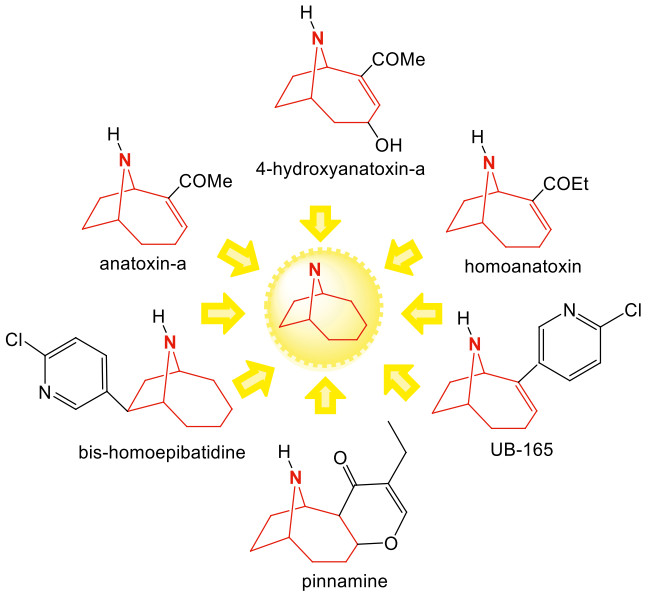



**Figure 1.** Some biologically active azacycles containing the 9-azabicyclo[4.2.1]nonane backbone.

fragment of the cholesterol molecule, an important natural steroid (Scheme 2). It should be noted that cholesterol performs a wide range of key functions in the body: it opens the biosynthetic chain of steroid hormones and corticosteroids and serves as the basis for the formation of bile acids and D vitamins, including the presence in the cell membranes, ensuring their stability.[11] Therefore, we consider heterocarbocycles, prepared on the basis of *N*-carbocholesteroxyazepine, as valuable precursors in the targeted synthesis of new drugs and other practically important biologically active molecules.

Thus, in order to develop an urgent line of research on the development of efficient methods for the synthesis of previously undescribed cholesteryl-containing 9-azabicyclo[4.2.1]nonadi(tri)enes, in this work, we have first studied the catalytic cycloaddition of 1,2-dienes and 1,3-diynes to *N*-carbocholesteroxyazepine (Scheme 2).

## RESULTS AND DISCUSSION

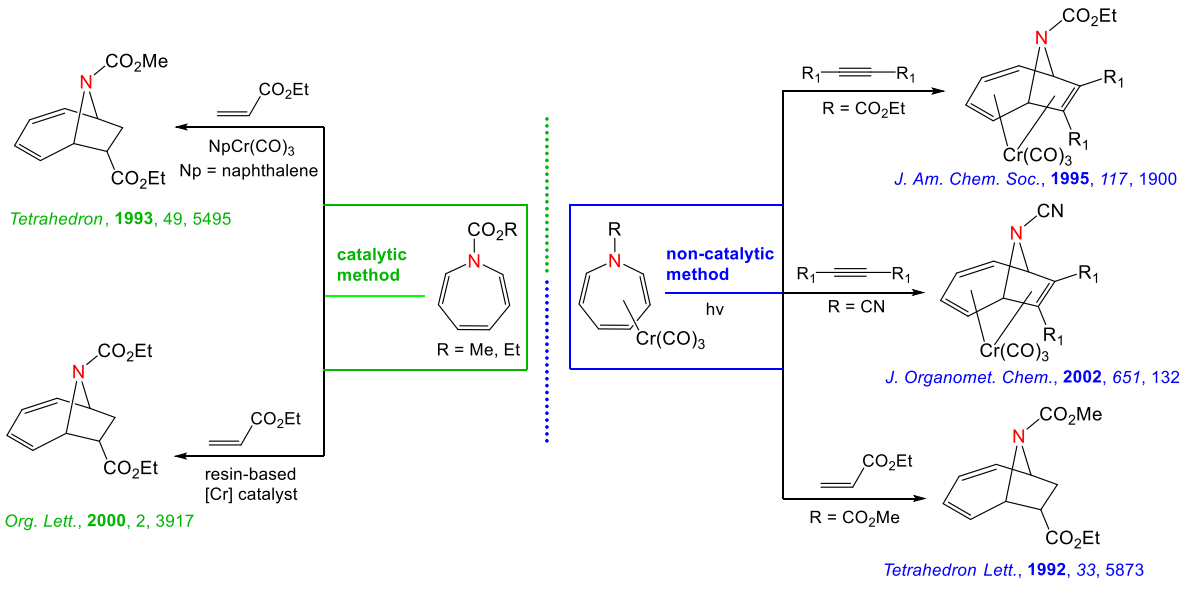
Initially, we have found that [6$\pi$ + 2$\pi$] cycloaddition of terminal 1,2-dienes **2a−e** (including functionally substituted ones) to *N*-carbocholesteroxyazepine **1** under the action of the three-component catalytic system $Co(acac)_2$(dppe)/Zn/$ZnI_2$,[12] under the developed conditions (10 mol % $Co(acac)_2$(dppe), 30 mol % Zn, 20 mol % $ZnI_2$, DCE (1,2-dichloroethane), 20 h, 60 °C), proceeds to produce substituted (*E*)-9-azabicyclo[4.2.1]nona-2,4-dienes **3a−e** in 79−92% yields. A double set of signals in a 1:1 ratio corresponding to two N−(CO)O−cholesteryl rotamers are registered in the ($^1$H and $^{13}$C) NMR spectra of cycloadducts **3a−e**, emerging as a result of limited rotation of the substituents around the C−N bond[1,6c,d,10] (Table 1).

In this case, both rotamers of cycloadducts **3a,c−e** are characterized by the (*E*)-configuration of the exocyclic C(7)−C(10) double bond, as confirmed by the presence of cross-peaks between the methylene protons $H_2C(8)$ and $H_2C(11)$ in the NOESY spectra (Figure 2).

Similar nuclear Overhauser effects are observed between the *ortho*-positioned protons $H_{ortho}$ of the phenyl group and $H_2C(8)$ protons for compound **3b**, indicating the (*E*)-configuration of the exo-double bond C(7)−C(10) (Figure 3).

Based on the observed data, we have tested the possibility of carrying out the reaction of catalytic cycloaddition of symmetric hexyl- and cyclopropyl-substituted 1,3-diynes, including those containing hydroxyl, sulfide, and trimethylsilyl functional groups, to *N*-carbocholesteroxyazepine **1**. We have found that the interaction of *N*-carbocholesteroxyazepine **1** with 1,3-diynes **4a−e** in the presence of the $Co(acac)_2$(dppe)/Zn/$ZnI_2$ catalytic system (10 mol % $Co(acac)_2$(dppe), 30 mol % Zn, 20 mol % $ZnI_2$, and $C_2H_4Cl_2$, 20 h, 60 °C) resulted in the formation of [6$\pi$ + 2$\pi$] cycloadducts, namely, substituted 9-azabicyclo[4.2.1]nona-2,4,7-trienes **5a−e** in high yields (77−90%). Similar to the abovementioned reaction of *N*-carbocholesteroxyazepine with 1,2-dienes, 9-azabicyclo[4.2.1]-

**Scheme 1. Catalytic and Noncatalytic [6$\pi$ + 2$\pi$] Cycloadditions of N-Substituted Azepines in the Synthesis of 9-Azabicyclo[4.2.1]nonadi(tri)enes**



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**Scheme 2. Schematic View of the Goals of Our Investigation in Comparison with Previously Published Data**

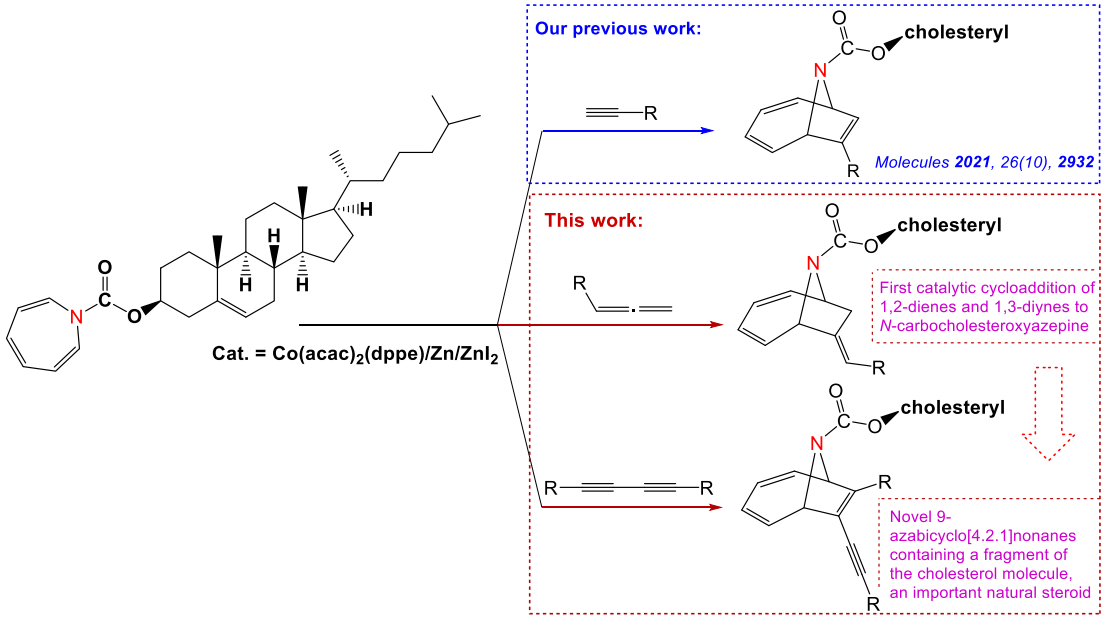
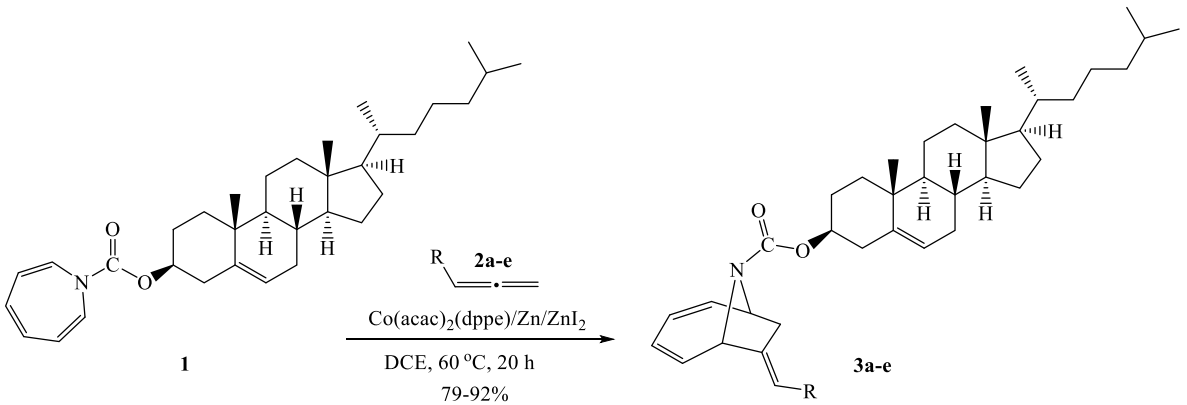



**Table 1. Cobalt(I)-Catalyzed [6π + 2π] Cycloaddition of 1,2-Dienes 2a−e to *N*-Carbocholesteroxyazepine[a]**




| entry | 1,2-diene | R | product | yield[b] (%) |
|---|---|---|---|---|
| 1 | **2a** | Hex | **3a** | 92 |
| 2 | **2b** | Ph | **3b** | 86 |
| 3 | **2c** | Bn | **3c** | 89 |
| 4 | **2d** | (CH2)4OH | **3d** | 79 |
| 5 | **2e** | (CH2)4Br | **3e** | 84 |

[a]Reaction conditions: **1** (1 mmol), **2** (1.5 mmol), $Co(acac)_2(dppe)$ (0.10 mmol), Zn (0.3 mmol), $ZnI_2$ (0.20 mmol), and DCE (3 mL), 60 °C, 20 h. [b]Yields of products isolated by column chromatography.

nona-2,4,7-trienes **5a−e** are formed as two N−(CO)O−cholesteryl conformational stereoisomers in a 1:1 ratio (Table 2).

## CONCLUSIONS

Thus, we have performed for the first time [6π + 2π] cycloaddition reactions of terminal 1,2-dienes and symmetric 1,3-diynes to *N*-carbocholesteroxyazepine under the action of the $Co(acac)_2(dppe)/Zn/ZnI_2$ three-component catalytic system to produce previously unreported heterofunctional (*E*)-9-azabicyclo[4.2.1]nona-2,4-dienes (79−92%) and 9-azabicyclo[4.2.1]nona-2,4,7-trienes (77−90%), covalently bound to an important natural metabolite, cholesterol.

## EXPERIMENTAL SECTION

**General Information.** The $^1H$ and $^{13}C$ spectra were measured in $CDCl_3$ on a Bruker AVANCE-500 spectrometer (500 MHz for $^1H$ and 125 MHz for $^{13}C$). High-resolution mass spectroscopy (HRMS) spectra were measured on an instrument ("MaXis impact", Bruker) using a time-of-flight mass analyzer (TOF) with electrospray ionization (ESI). In experiments on selective collisional activation, the activation energy was set at maximum abundance of fragment peaks. A syringe injection was used for solutions in MeCN (flow rate 5 μL/min). Nitrogen was applied as a dry gas; the interface temperature was set at 180 °C. All solvents were dried and freshly distilled before use. All reactions were carried out under a dry argon atmosphere. *N*-Carbocholesteroxyazepine was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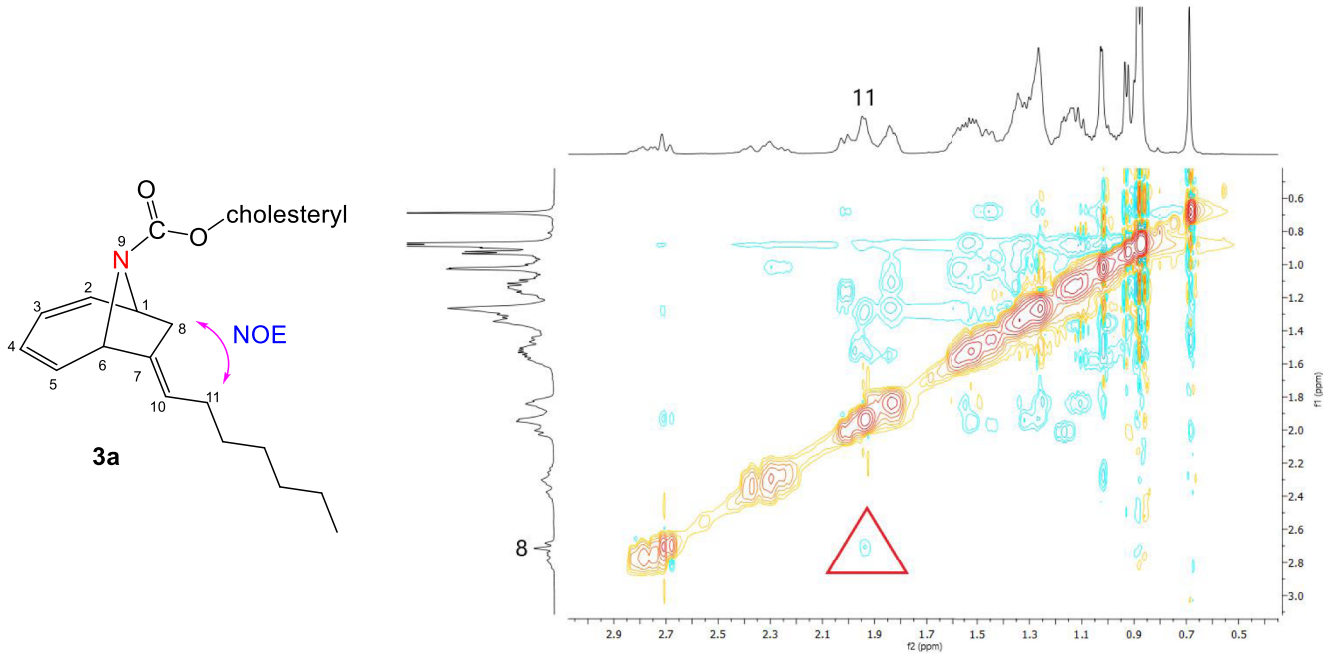


**Figure 2.** Fragment of the 2D NOESY-GPPH spectrum for compound **3a**.

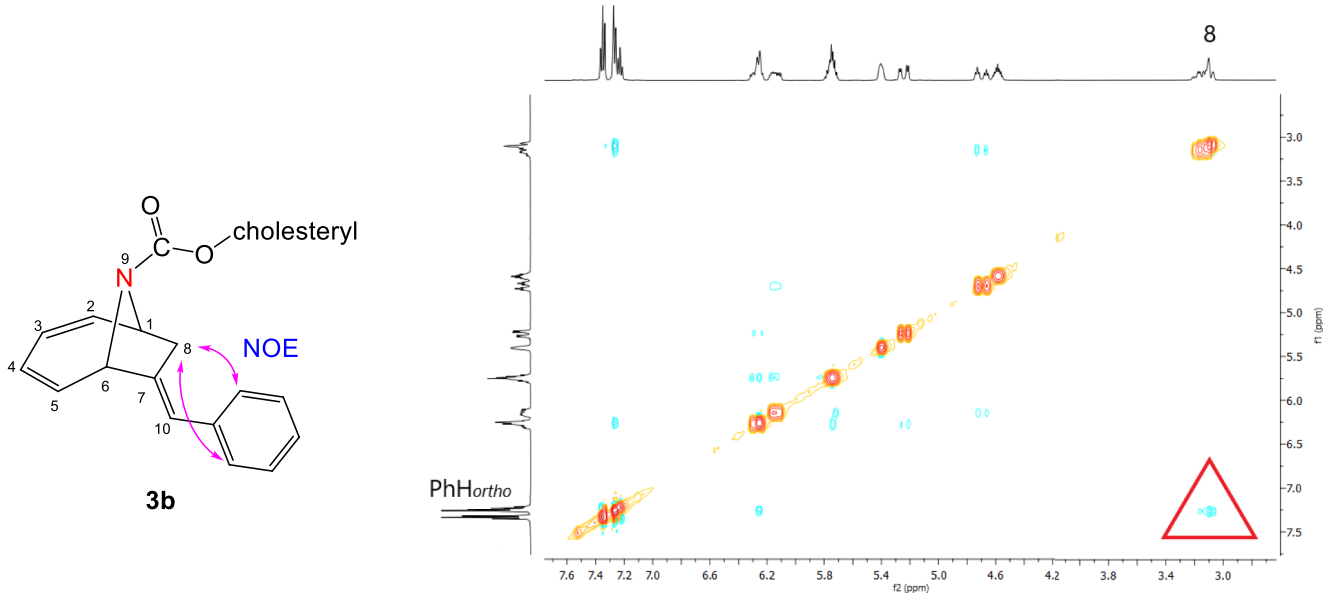


**Figure 3.** Fragment of the 2D NOESY-GPPH spectrum for compound **3b**.

synthesized according to reported procedures.[10] 1,2-Dienes, 1,3-diynes, and $Co(acac)_2(dppe)$ were synthesized according to procedures described in the literature.[13]

**Cycloaddition of 1,2-Dienes and 1,3-Diynes to *N*-Carbocholesteroxyazepine (General Reaction Procedure).** Zinc powder (30 mol %) was added to a solution of $Co(acac)_2(dppe)$ (10 mol %) in DCE (1.5 mL) in a Schlenk tube under a dry argon atmosphere, and the mixture was stirred at room temperature for 2 min. Next, *N*-carbocholesteroxyazepine (1.0 mmol), the 1,2-diene (or the 1,3-diyne) (1.5 mmol) in DCE (1.5 mL), and dry $ZnI_2$ (20 mol %) ($ZnI_2$ was weighed in a dry weighing bottle) were added successively. After heating at 60 °C for 20 h, the reaction was stopped by the addition of petroleum ether and stirring in air for 10 min to deactivate the catalyst. After filtration through a short pad of silica, the volatiles were removed under vacuum. Chromatographic purification over silica gel (petroleum ether/ethyl acetate 5:1) afforded the target products **3a**−**e** and **5a**−**e**.

*Cholesteryl (1S*,6R*)-7-[(E)Heptylidene]-9-azabicyclo-[4.2.1]nona-2,4-diene-9-carboxylate Equivalent with Cholesteryl (1R*,6S*)-7-[(E)Heptylidene]-9-azabicyclo[4.2.1]-nona-2,4-diene-9-carboxylate (**3a**).* Yield 92% (0.580 g), yellowish solid, mp 103−104 °C, $[\alpha]_D24$ −11.6 (*c* 0.50, $CH_2Cl_2$), exists as two N−(CO)O−cholesteryl rotamers. $R_f$ = 0.43 (petroleum ether/ethyl acetate 5:1). $^1H$ NMR (500 MHz, $CDCl_3$): $\delta$ 6.03−6.23 (m, 4H), 5.62−5.73 (m, 4H), 5.37 (d, *J* = 5.8 Hz, 2H), 5.19 (d, *J* = 7.5 Hz, 2H), 5.03 (d, *J* = 5.4 Hz, 1H), 4.98 (d, *J* = 5.5 Hz, 1H), 4.47−4.66 (m, 4H), 2.66−2.86 (m, 4H), 2.19−2.45 (m, 4H), 1.79−2.07 (m, 14H), 0.97−1.63 (m, 62H), 0.93 (d, *J* = 6.4 Hz, 5H), 0.88 (d, *J* = 6.7 Hz, 21H),


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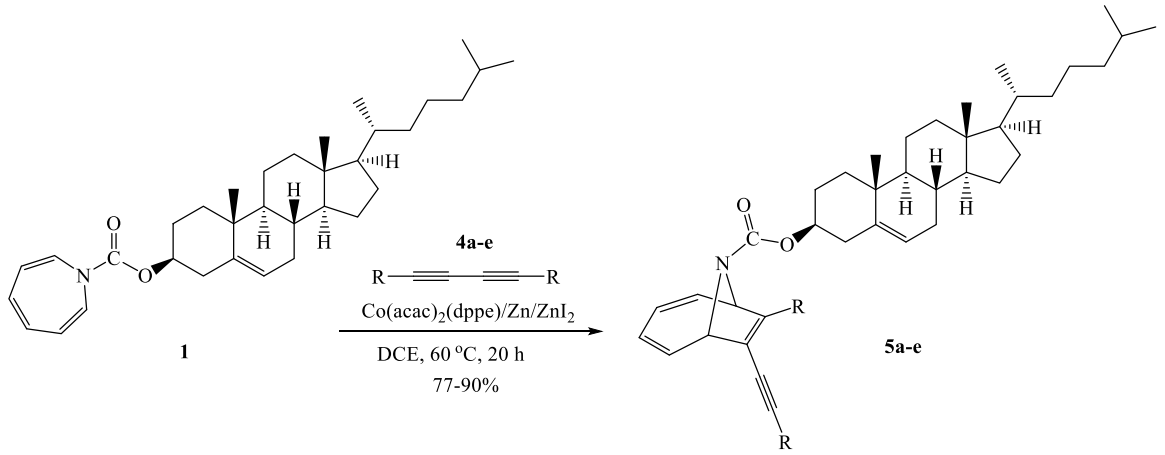
Table 2. Cobalt(I)-Catalyzed [6π + 2π] Cycloaddition of 1,3-Diynes 4a−e to *N*-Carbocholesteroxyazepine[a]




| entry | 1,3-diyne | R | product | yield[b] (%) |
|---|---|---|---|---|
| 1 | **4a** | Hex | **5a** | 90 |
| 2 | **4b** | $SiMe_3$ | **5b** | 88 |
| 3 | **4c** | $(CH_2)_2OH$ | **5c** | 78 |
| 4 | **4d** | $(CH_2)_3SBu^t$ | **5d** | 83 |
| 5 | **4e** | $CH(CH_2)_2$ | **5e** | 77 |

[a]Reaction conditions: **1** (1 mmol), **4** (1.5 mmol), $Co(acac)_2(dppe)$ (0.10 mmol), Zn (0.3 mmol), $ZnI_2$ (0.20 mmol), and DCE (3 mL), 60 °C, 20 h. [b]Yields of products isolated by column chromatography.

0.69 (s, 6H) ppm. $^{13}C$ NMR (125 MHz, $CDCl_3$): δ 154.2 (2C), 146.3, 145.4, 140.0 (2C), 138.1 (2C), 137.7 (2C), 123.6 (2C), 123.4 (2C), 122.4, 122.3, 121.9 (2C), 74.5 (2C), 60.7, 60.6, 56.7 (2C), 56.69 (2C), 56.1 (2C), 50.0 (2C), 42.3 (2C), 41.7 (2C), 39.8 (2C), 39.5 (2C), 38.7, 38.4, 37.0, 36.98, 36.6 (2C), 36.2 (2C), 35.8 (2C), 31.9 (4C), 31.7 (2C), 29.3 (2C), 29.1 (2C), 28.9 (2C), 28.2 (4C), 28.0 (2C), 24.3 (2C), 23.9 (2C), 22.8 (2C), 22.6 (2C), 22.57 (2C), 21.1 (2C), 19.4 (2C), 18.7 (2C), 14.1 (2C), 11.9 (2C) ppm. HRMS (ESI-TOF): calcd for $C_{43}H_{67}NO_2Na$ $[M + Na]^+$, 652.5069; found, 652.5078.

*Cholesteryl (1S*,6R*)-7-[(E)-Phenylmethylidene]-9-azabicyclo[4.2.1]nona-2,4-diene-9-carboxylate Equivalent with Cholesteryl (1R*,6S*)-7-[(E)-Phenylmethylidene]-9-azabicyclo[4.2.1]nona-2,4-diene-9-carboxylate (**3b**).* Yield 86% (0.535 g), yellowish solid, mp 108−109 °C, $[\alpha]_D24$ −12.6 (*c* 0.49, $CH_2Cl_2$), exists as two N−(CO)O−cholesteryl rotamers. $R_f$ = 0.45 (petroleum ether/ethyl acetate 5:1). $^1H$ NMR (500 MHz, $CDCl_3$): δ 7.35 (t, *J* = 7.6 Hz, 4H), 7.21−7.29 (m, 6H), 6.22−6.33 (m, 4H), 6.09−6.20 (m, 2H), 5.70−5.80 (m, 4H), 5.40 (s, 2H), 5.27 (d, *J* = 5.9 Hz, 1H), 5.22 (d, *J* = 6.0 Hz, 1H), 4.73 (t, *J* = 6.5 Hz, 1H), 4.67 (t, *J* = 6.7 Hz, 1H), 4.54−4.63 (m, 2H), 3.05−3.23 (m, 4H), 2.24−2.48 (m, 4H), 1.82−2.08 (m, 10H), 1.25−1.66 (m, 22H), 1.09−1.24 (m, 14H), 1.00−1.08 (m, 10H), 0.96 (d, *J* = 6.5 Hz, 8H), 0.91 (d, *J* = 2.1 Hz, 6H), 0.90 (d, *J* = 2.2 Hz, 6H), 0.71 (s, 6H) ppm. $^{13}C$ NMR (125 MHz, $CDCl_3$): δ 154.1 (2C), 148.4, 147.5, 139.9 (2C), 137.8, 137.7, 137.4 (2C), 137.3, 137.27, 128.4 (4C), 128.1 (4C), 126.7 (2C), 124.2 (2C), 123.9 (2C), 122.5, 122.4, 121.6 (2C), 74.7 (2C), 62.3, 62.1, 57.2, 57.15, 56.7 (2C), 56.2 (2C), 50.0 (2C), 43.9, 43.4, 42.3 (2C), 39.8 (2C), 39.6 (2C), 38.7, 38.5, 37.1, 37.0, 36.6 (2C), 36.2 (2C), 35.8 (2C), 31.94 (2C), 31.9 (2C), 28.3 (3C), 28.2, 28.0 (2C), 24.3 (2C), 23.9 (2C), 22.9 (2C), 22.6 (2C), 21.1 (2C), 19.4 (2C), 18.8 (2C), 11.9 (2C) ppm. HRMS (ESI-TOF): calcd for $C_{43}H_{59}NO_2Na$ $[M + Na]^+$, 644.4443: found, 644.4438.

*Cholesteryl (1S*,6R*)-7-[(E)-2-Phenylethylidene]-9-azabicyclo[4.2.1]nona-2,4-diene-9-carboxylate Equivalent with Cholesteryl (1R*,6S*)-7-[(E)-2-Phenylethylidene]-9-azabicyclo[4.2.1]nona-2,4-diene-9-carboxylate (**3c**).* Yield 89% (0.566 g), yellowish solid, mp 143−144 °C, $[\alpha]_D24$ −32.4 (*c* 0.50, $CH_2Cl_2$), exists as two N−(CO)O−cholesteryl rotamers. $R_f$ = 0.41 (petroleum ether/ethyl acetate 5:1). $^1H$ NMR (500 MHz, $CDCl_3$): δ 7.30 (t, *J* = 7.3 Hz, 4H), 7.22 (t, *J* = 7.1 Hz, 2H), 7.17 (d, *J* = 7.4 Hz, 4H), 6.09−6.28 (m, 4H), 5.69−5.82 (m, 4H), 5.35−5.48 (m, 4H), 5.13 (d, *J* = 5.1 Hz, 1H), 5.08 (d, *J* = 5.4 Hz, 1H), 4.52−4.72 (m, 4H), 3.34 (s, 4H), 2.81−2.98 (m, 4H), 2.24−2.47 (m, 4H), 1.81−2.09 (m, 10H), 1.25−1.66 (m, 22H), 1.09−1.24 (m, 14H), 1.00−1.09 (m, 10H), 0.96 (d, *J* = 6.3 Hz, 8H), 0.91 (s, 6H), 0.90 (s, 6H), 0.72 (s, 6H) ppm. $^{13}C$ NMR (125 MHz, $CDCl_3$): δ 154.1 (2C), 147.6, 146.8, 140.3 (2C), 140.0 (2C), 137.9 (2C), 137.7 (2C), 128.5 (4C), 128.2 (4C), 126.1 (2C), 123.8 (4C), 122.4, 122.37, 120.2, 120.1, 74.6 (2C), 60.7, 60.6, 56.74 (2C), 56.7 (2C), 56.2 (2C), 50.0 (2C), 42.5, 42.3 (2C), 41.9, 39.8 (2C), 39.6 (2C), 38.7, 38.5, 37.0 (2C), 36.6 (2C), 36.2 (2C), 35.8 (2C), 35.5 (2C), 31.94 (2C), 31.9 (2C), 28.3 (4C), 28.1 (2C), 24.3 (2C), 23.9 (2C), 22.9 (2C), 22.6 (2C), 21.1 (2C), 19.4 (2C), 18.8 (2C), 11.9 (2C) ppm. HRMS (ESI-TOF): calcd for $C_{44}H_{61}NO_2Na$ $[M + Na]^+$, 658.4600; found, 658.4627.

*Cholesteryl (1S*,6R*)-7-[(E)-5-Hydroxypentylidene]-9-azabicyclo[4.2.1]nona-2,4-diene-9-carboxylate Equivalent with Cholesteryl (1R*,6S*)-7-[(E)-5-Hydroxypentylidene]-9-azabicyclo[4.2.1]nona-2,4-diene-9-carboxylate (**3d**).* Yield 79% (0.488 g), yellowish solid, mp 125−126 °C, $[\alpha]_D24$ −11.4 (*c* 0.50, $CH_2Cl_2$), exists as two N−(CO)O−cholesteryl rotamers. $R_f$ = 0.48 (petroleum ether/ethyl acetate 5:1). $^1H$ NMR (500 MHz, $CDCl_3$): δ 6.04−6.22 (m, 4H), 5.63−5.74 (m, 4H), 5.36 (d, *J* = 7.1 Hz, 2H), 5.20 (d, *J* = 7.9 Hz, 2H), 5.03 (d, *J* = 5.8 Hz, 1H), 4.99 (d, *J* = 5.9 Hz, 1H), 4.48−4.65 (m, 4H), 3.63 (t, *J* = 6.5 Hz, 4H), 2.67−2.86 (m, 4H), 2.20−2.42 (m, 4H), 1.79−2.07 (m, 14H), 1.22−1.63 (m, 30H),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1.05−1.21 (m, 14H), 0.97−1.04 (m, 10H), 0.93 (d, $J$ = 6.5 Hz, 8H), 0.88 (d, $J$ = 2.1 Hz, 6H), 0.87 (d, $J$ = 2.1 Hz, 6H), 0.69 (s, 6H) ppm. $^{13}$C NMR (125 MHz, $CDCl_3$): $\delta$ 154.2 (2C), 146.7, 145.9, 140.0 (2C), 138.0 (2C), 137.8 (2C), 123.6 (2C), 123.5 (2C), 122.4, 122.3, 121.4 (2C), 74.6 (2C), 62.7 (2C), 60.7, 60.5, 56.7 (4C), 56.1 (2C), 50.0 (2C), 42.3 (2C), 41.7 (2C), 39.7 (2C), 39.5 (2C), 38.7, 38.4, 37.0, 36.96, 36.6 (2C), 36.2 (2C), 35.8 (2C), 32.2 (2C), 31.9 (2C), 31.88 (2C), 29.0 (2C), 28.2 (4C), 28.0 (2C), 25.4 (2C), 24.3 (2C), 23.8 (2C), 22.8 (2C), 22.6 (2C), 21.0 (2C), 19.4 (2C), 18.7 (2C), 11.9 (2C) ppm. HRMS (ESI-TOF): calcd for $C_{41}H_{63}NO_3Na$ [M + Na]$^+$, 640.4705; found, 640.4706.

*Cholesteryl (1S*,6R*)-7-[(E)-5-Bromopentylidene]-9-azabicyclo[4.2.1]nona-2,4-diene-9-carboxylate Equivalent with Cholesteryl (1R*,6S*)-7-[(E)-5-Bromopentylidene]-9-azabicyclo[4.2.1]nona-2,4-diene-9-carboxylate (**3e**).* Yield 84% (0.572 g), yellowish solid, mp 95−96 °C, $[\alpha]D^{25}$ −11 ($c$ 0.50, $CH_2Cl_2$), exists as two N−(CO)O−cholesteryl rotamers. $R_f$ = 0.43 (petroleum ether/ethyl acetate 5:1). $^1$H NMR (500 MHz, $CDCl_3$): $\delta$ 6.04−6.26 (m, 4H), 5.63−5.78 (m, 4H), 5.38 (s, 2H), 5.19 (s, 2H), 5.05 (s, 1H), 5.00 (s, 1H), 4.48−4.69 (m, 4H), 3.40 (t, $J$ = 6.1 Hz, 4H), 2.66−2.87 (m, 4H), 2.20−2.44 (m, 4H), 1.79−2.10 (m, 14H), 0.96−1.68 (m, 54H), 0.93 (d, $J$ = 5.8 Hz, 8H), 0.88 (d, $J$ = 5.4 Hz, 12H), 0.69 (s, 6H) ppm. $^{13}$C NMR (125 MHz, $CDCl_3$): $\delta$ 154.1 (2C), 147.1, 146.3, 140.0 (2C), 138.0 (2C), 137.7 (2C), 123.7 (2C), 123.6 (2C), 122.4, 122.3, 121.0 (2C), 74.6 (2C), 60.6, 60.5, 56.7 (4C), 56.1 (2C), 50.0 (2C), 42.3 (2C), 41.8 (2C), 39.7 (2C), 39.5 (2C), 38.7, 38.4, 37.0, 36.97, 36.6 (2C), 36.2 (2C), 35.8 (2C), 33.6 (2C), 32.2 (2C), 31.9 (4C), 28.4 (2C), 28.2 (4C), 28.0 (2C), 27.7 (2C), 24.3 (2C), 23.8 (2C), 22.8 (2C), 22.6 (2C), 21.1 (2C), 19.4 (2C), 18.7 (2C), 11.9 (2C) ppm. HRMS (ESI-TOF): calcd for $C_{41}H_{62}BrNO_2Na$ [M + Na]$^+$, 702.3861; found, 702.3903.

*Cholesteryl (1S*,6R*)-7-Hexyl-8-(oct-1-yn-1-yl)-9-azabicyclo[4.2.1]nona-2,4,7-triene-9-carboxylate Equivalent with Cholesteryl (1R*,6S*)-7-Hexyl-8-(oct-1-yn-1-yl)-9-azabicyclo[4.2.1]nona-2,4,7-triene-9-carboxylate (**5a**).* Yield 90% (0.652 g), yellowish solid, mp 96−97 °C, $[\alpha]_D$24 −9.4 ($c$ 0.50, $CH_2Cl_2$), exists as two N−(CO)O−cholesteryl rotamers. $R_f$ = 0.55 (petroleum ether/ethyl acetate 5:1). $^1$H NMR (500 MHz, $CDCl_3$): $\delta$ 6.33−6.44 (m, 2H), 6.20−6.31 (m, 2H), 5.87−5.96 (m, 4H), 5.36 (d, $J$ = 11.7 Hz, 2H), 4.95 (d, $J$ = 5.0 Hz, 1H), 4.83−4.89 (m, 3H), 4.43−4.52 (m, 2H), 2.34 (t, $J$ = 6.9 Hz, 6H), 2.21−2.32 (m, 6H), 1.76−2.06 (m, 10H), 1.23−1.62 (m, 54H), 0.85−1.22 (m, 56H), 0.69 (s, 6H) ppm. $^{13}$C NMR (125 MHz, $CDCl_3$): $\delta$ 153.1 (2C), 142.4 (2C), 139.9 (2C), 139.1 (2C), 138.2 (2C), 124.8 (2C), 124.0 (2C), 122.4 (2C), 113.8 (2C), 95.1, 94.9, 74.5 (2C), 72.9 (2C), 62.8, 62.6, 62.0, 61.9, 56.7 (2C), 56.1 (2C), 50.0 (2C), 42.3 (2C), 39.7 (2C), 39.5 (2C), 38.6, 38.4, 37.0 (2C), 36.5 (2C), 36.2 (2C), 35.8 (2C), 31.9 (4C), 31.5 (2C), 31.3 (2C), 29.0 (2C), 28.8, 28.7 (3C), 28.5 (2C), 28.2 (4C), 28.0 (2C), 26.3, 26.1, 24.3 (2C), 23.8 (2C), 22.8 (2C), 22.6 (6C), 21.0 (2C), 19.6 (2C), 19.4 (2C), 18.7 (2C), 14.1 (2C), 14.0 (2C), 11.9 (2C) ppm. HRMS (ESI-TOF): calcd for $C_{50}H_{77}NO_2Na$ [M + Na]$^+$, 746.5852; found, 746.5860.

*Cholesteryl (1S*,6R*)-7-(Trimethylsilyl)-8-((trimethylsilyl)-ethynyl)-9-azabicyclo[4.2.1]nona-2,4,7-triene-9-carboxylate equivalent with Cholesteryl (1R*,6S*)-7-(Trimethylsilyl)-8-((trimethylsilyl)ethynyl)-9-azabicyclo[4.2.1]nona-2,4,7-triene-9-carboxylate (**5b**).* Yield 88% (0.616 g), yellowish solid, mp 93−94 °C, $[\alpha]_D$24 −11.4 ($c$ 0.50, $CH_2Cl_2$), exists as two N−(CO)O−cholesteryl rotamers. $R_f$ = 0.52 (petroleum ether/ethyl acetate 5:1). $^1$H NMR (500 MHz, $CDCl_3$): $\delta$ 6.29−6.39 (m, 2H), 6.23−6.29 (m, 1H), 6.20 (dd, $J$ = 10.9 Hz, $J$ = 5.3 Hz, 1H), 5.90−6.05 (m, 4H), 5.32−5.39 (m, 2H), 5.04 (dd, $J$ = 7.3 Hz, $J$ = 5.7 Hz, 2H), 4.96 (dd, $J$ = 5.3 Hz, $J$ = 1.4 Hz, 1H), 4.86 (d, $J$ = 5.3 Hz, 1H), 4.43−4.52 (m, 2H), 2.19−2.40 (m, 4H), 1.93−2.07 (m, 4H), 1.75−1.91 (m, 6H), 1.23−1.63 (m, 22H), 0.96−1.22 (m, 24H), 0.93 (d, $J$ = 6.5 Hz, 8H), 0.89 (d, $J$ = 2.2 Hz, 6H), 0.88 (d, $J$ = 2.1 Hz, 6H), 0.69 (s, 6H), 0.23 (s, 18H), 0.20 (s, 18H) ppm. $^{13}$C NMR (125 MHz, $CDCl_3$): $\delta$ 152.9 (2C), 142.3 (2C), 139.9 (2C), 137.5 (2C), 137.1 (2C), 124.9 (2C), 124.5 (2C), 122.4, 122.3, 99.4, 99.3, 99.2, 99.0, 74.6, 74.5, 64.4, 64.3, 64.2, 63.9, 56.7 (2C), 56.1 (2C), 50.0 (2C), 42.3 (2C), 39.7 (2C), 39.5 (2C), 38.6, 38.4, 37.0 (2C), 36.5 (2C), 36.2 (2C), 35.8 (2C), 31.9 (4C), 28.2 (4C), 28.0 (2C), 24.3 (2C), 23.8 (2C), 22.8 (2C), 22.6 (2C), 21.0 (2C), 19.4 (2C), 18.7 (2C), 11.9 (2C), −0.3 (6C), −0.9 (6C) ppm. HRMS (ESI-TOF): calcd for $C_{44}H_{69}NO_2Si_2Na$ [M + Na]$^+$, 722.4764; found, 722.4789.

*Cholesteryl (1S*,6R*)-7-(4-Hydroxybut-1-yn-1-yl)-8-(2-hydroxyethyl)-9-azabicyclo[4.2.1]nona-2,4,7-triene-9-carboxylate Equivalent with Cholesteryl (1R*,6S*)-7-(4-Hydroxybut-1-yn-1-yl)-8-(2-hydroxyethyl)-9-azabicyclo[4.2.1]nona-2,4,7-triene-9-carboxylate (**5c**).* Yield 78% (0.502 g), yellowish solid, mp 162−163 °C, $[\alpha]_D$24 −11.6 ($c$ 0.50, $CH_2Cl_2$), exists as two N−(CO)O−cholesteryl rotamers. $R_f$ = 0.59 (petroleum ether/ethyl acetate 5:1). $^1$H NMR (500 MHz, $CDCl_3$): $\delta$ 6.25−6.45 (m, 4H), 5.95 (s, 4H), 5.35 (d, $J$ = 9.5 Hz, 2H), 4.98 (d, $J$ = 4.0 Hz, 1H), 4.87−4.95 (m, 3H), 4.46 (s, 2H), 3.71−3.80 (m, 8H), 2.49−2.64 (m, 8H), 2.17−2.37 (m, 4H), 1.91−2.05 (m, 4H), 1.73−1.90 (m, 6H), 1.22−1.62 (m, 22H), 1.04−1.21 (m, 14H), 0.98−1.03 (m, 10H), 0.92 (d, $J$ = 6.4 Hz, 8H), 0.87 (d, $J$ = 6.6 Hz, 12H), 0.68 (s, 6H) ppm. $^{13}$C NMR (125 MHz, $CDCl_3$): $\delta$ 153.0 (2C), 139.8 (2C), 139.2 (2C), 139.1, 138.9, 137.9 (2C), 125.3 (2C), 124.3 (2C), 122.5, 122.45, 115.1, 114.9, 92.3, 92.1, 74.8 (2C), 74.4 (2C), 62.6, 62.4, 62.3, 62.2, 61.3 (2C), 60.9 (2C), 56.7 (2C), 56.1 (2C), 50.0 (2C), 42.3 (2C), 39.7 (2C), 39.5 (2C), 38.5, 38.4, 37.0 (2C), 36.5 (2C), 36.2 (2C), 35.8 (2C), 31.9 (2C), 31.86 (2C), 30.0, 29.8, 28.2 (3C), 28.15, 28.0 (2C), 24.3 (2C), 24.0 (2C), 23.8 (2C), 22.8 (2C), 22.6 (2C), 21.0 (2C), 19.4 (2C), 18.7 (2C), 11.9 (2C) ppm. HRMS (ESI-TOF): calcd for $C_{42}H_{61}NO_4Na$ [M + Na]$^+$, 666.4498; found, 666.4508.

*Cholesteryl (1S*,6R*)-7-(5-(tert-Butylthio)pent-1-yn-1-yl)-8-(3-(tert-butylthio)propyl)-9-azabicyclo[4.2.1]nona-2,4,7-triene-9-carboxylate Equivalent with Cholesteryl (1R*,6S*)-7-(5-(tert-Butylthio)pent-1-yn-1-yl)-8-(3-(tert-butylthio)-propyl)-9-azabicyclo[4.2.1]nona-2,4,7-triene-9-carboxylate (**5d**).* Yield 83% (0.678 g), yellowish solid, mp 172−173 °C, $[\alpha]_D$24 −10.4 ($c$ 0.50, $CH_2Cl_2$), exists as two N−(CO)O−cholesteryl rotamers. $R_f$ = 0.57 (petroleum ether/ethyl acetate 5:1). $^1$H NMR (500 MHz, $CDCl_3$): $\delta$ 6.20−6.43 (m, 4H), 5.85−5.97 (m, 4H), 5.35 (d, $J$ = 9.5 Hz, 2H), 4.93 (d, $J$ = 4.4 Hz, 1H), 4.80−4.91 (m, 3H), 4.40−4.52 (m, 2H), 2.65 (t, $J$ = 7.1 Hz, 4H), 2.18−2.57 (m, 16H), 1.73−2.06 (m, 18H), 0.96−1.62 (m, 82H), 0.92 (d, $J$ = 6.1 Hz, 8H), 0.87 (d, $J$ = 5.6 Hz, 12H), 0.68 (s, 6H) ppm. $^{13}$C NMR (125 MHz, $CDCl_3$): $\delta$ 153.0 (2C), 141.3 (2C), 139.8 (2C), 139.0 (2C), 138.0 (2C), 125.0 (2C), 124.1 (2C), 122.4 (2C), 114.2, 114.1, 94.3, 94.2, 74.6 (2C), 73.4 (2C), 62.8, 62.6, 62.1 (2C), 56.7 (2C), 56.1 (2C), 50.0 (2C), 42.3 (2C), 42.1 (2C), 42.0 (2C), 39.7 (2C), 39.5 (2C), 38.6, 38.4, 36.9 (2C), 36.5 (2C), 36.2 (2C), 35.8 (2C), 31.9 (4C), 31.0 (12H), 29.2 (2C), 29.0, 28.9, 28.2 (3C),


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28.1, 28.0 (2C), 27.9, 27.8, 27.3, 27.29, 26.0 (2C), 24.3 (2C), 23.8 (2C), 22.8 (2C), 22.6 (2C), 21.0 (2C), 19.4 (2C), 19.0 (2C), 18.7 (2C), 11.9 (2C) ppm. HRMS (ESI-TOF): calcd for $C_{52}H_{81}NO_2S_2Na$ $[M + Na]^+$, 838.5606; found, 838.5625.

*Cholesteryl (1S*,6R*)-7-Cyclopropyl-8-(cyclopropylethynyl)-9-azabicyclo[4.2.1]nona-2,4,7-triene-9-carboxylate Equivalent with Cholesteryl (1R*,6S*)-7-Cyclopropyl-8-(cyclopropylethynyl)-9-azabicyclo[4.2.1]nona-2,4,7-triene-9-carboxylate (**5e**).* Yield 77% (0.490 g), yellowish solid, mp 110−111 °C, $[\alpha]_D24$ −9.5 (*c* 0.50, $CH_2Cl_2$), exists as two N−(CO)O−cholesteryl rotamers. $R_f$ = 0.55 (petroleum ether/ethyl acetate 5:1). $^1H$ NMR (500 MHz, $CDCl_3$): $\delta$ 6.31−6.42 (m, 2H), 6.07−6.18 (m, 2H), 5.85−5.93 (m, 4H), 5.35 (d, $J$ = 12.8 Hz, 2H), 4.82 (t, $J$ = 5.9 Hz, 2H), 4.69 (d, $J$ = 5.2 Hz, 1H), 4.62 (d, $J$ = 5.2 Hz, 1H), 4.42−4.50 (m, 2H), 2.16−2.41 (m, 4H), 1.72−2.06 (m, 10H), 1.63−1.71 (m, 2H), 1.22−1.62 (m, 24H), 0.78−1.21 (m, 54H), 0.72−0.76 (m, 4H), 0.68 (s, 6H), 0.55−0.62 (m, 2H) ppm. $^{13}C$ NMR (125 MHz, $CDCl_3$): $\delta$ 153.0 (2C), 145.1 (2C), 139.8 (2C), 139.1, 138.9, 138.2 (2C), 124.7 (2C), 123.9 (2C), 122.4 (2C), 113.0 (2C), 98.4 (2C), 98.2 (2C), 74.6 (2C), 63.2, 63.0, 60.5, 60.4, 56.7 (2C), 56.1 (2C), 50.0 (2C), 42.3 (2C), 39.7 (2C), 39.5 (2C), 38.6, 38.4, 36.9 (2C), 36.5 (2C), 36.2 (2C), 35.8 (2C), 31.9 (4C), 28.2 (3C), 28.15, 28.0 (2C), 24.3 (2C), 23.8 (2C), 22.8 (2C), 22.6 (2C), 21.0 (2C), 19.4 (2C), 18.7 (2C), 11.9 (2C), 10.1, 9.9, 9.0 (2C), 8.8 (2C), 8.7 (2C), 7.0, 6.9, 0.4 (2C) ppm. HRMS (ESI-TOF): calcd for $C_{44}H_{61}NO_2Na$ $[M + Na]^+$, 658.4600; found, 658.4601.

## ■ ASSOCIATED CONTENT

### Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acsomega.1c03321.

Copies of $^1H$, $^{13}C$ NMR spectra for all compounds (PDF)

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