Stereocontrolled Synthesis of Key Advanced Intermediates toward Simplified Acetogenin Analogues

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Received May 11, 1999

The stereo- and enantiocontrolled synthesis of substituted β-hydroxy ethers based on glycol and catechol bearing an alkyne group and a series of substituents is reported. These substrates were designed to mimic the bis-THF array of annonaceous acetogenins and to provide an access to simplified and modified analogues. The key steps of the synthesis involve the condensation of the nonracemic mesylate of solketal with ethylene glycol and catechol, followed by an alkylation with a glycidyl derivative. Under appropriate conditions, the reaction is completely stereoselective and allows the synthesis of all the diastereomers. After the epoxide was opened with triethylsilylacetylene, the second epoxide was unmasked and reacted with a series of alkyl, aryl, amine, and alcohol reagents. A series of 28 analogues was prepared having a glycol or a catechol core, a stereodefined configuration of the flanking hydroxyl groups, and an acetylenic appendage suitable for a coupling to a lactone-bearing fragment.

Introduction

The Annonaceae form a large family of trees, shrubs, or lianas commonly found in tropical and subtropical areas.[1] The medicinal, cosmetic and culinary values[2] of these plants have been recognized by the indigenous populations for a long time: the leaves, roots, bark, or fruits have been used in various preparations for the treatment of numerous ailments such as sleep disorder and fever, as an antiseptic, or against fungi or parasitic infestations.[3] Since the isolation of the first acetogenin uvaricine **1** by Jollad et al.,[4] over 230 new acetogenins have been discovered and their broad spectrum of activity revealed: antitumoral, antimalarial, pesticidal, antibacterial, or immunosuppressive.[5] Their very potent cytotoxicity (often nM) has made them a promising new lead for cancer chemotherapy[6] and possibly against multidrug-resistant cell ligns.[7] Some of the acetogenins have been shown to be strong inhibitors of the NADH: ubiquinone reductase (complex I) in the mitochondrial membrane and of the NADH oxidase in the plasmic membrane.[8] This interference with respiration and ATP production leads to the rapid death of the cell. The acetogenins, however, do not appear to be inhibitors of tyrosine kinase; they have no action on the cell cycle and have no DNA-damaging effects.[9]

Considering the potential of this class of compounds as therapeutic agents or as biological tools and the important synthetic efforts reported to date,[10] we found it surprising that little attention had been paid so far to find out the relative contributions of the various constitutional parts of the molecule to the biological activity.[11] We initiated a program toward the synthesis of simplified and modified acetogenin analogues, the final aim being to better understand the structure−activity relationships.

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10.1021/jo990772h CCC: $18.00
Published on Web 08/17/1999

Among the five subfamilies of acetogenins the B1 subtype (adjacent bis-THF)[12] represents the most potent and has been intensely studied. The structures and the relative stereochemistries have been established by partial or total synthesis, by NMR analysis, Mosher ester techniques,[13] and/or combinations thereof.[14] This class was thus chosen as the model system for this study.

The length and difficulties inherent to the synthesis of the central bis-THF unit is well documented. Thus, the first objective was to develop an efficient synthesis of simpler bis-ether analogues (Figure 1).

This simplification should, in the end, shed some light on the importance of the rigidity of the system, which might be important if the recognized cation sequestration ability of these compounds plays indeed a role in the mechanism of action, membrane transit, and molecular recognition.[15] The second objective we deemed necessary to achieve was the control of the stereochemistry of the flanking hydroxyl groups. As we have learned from the

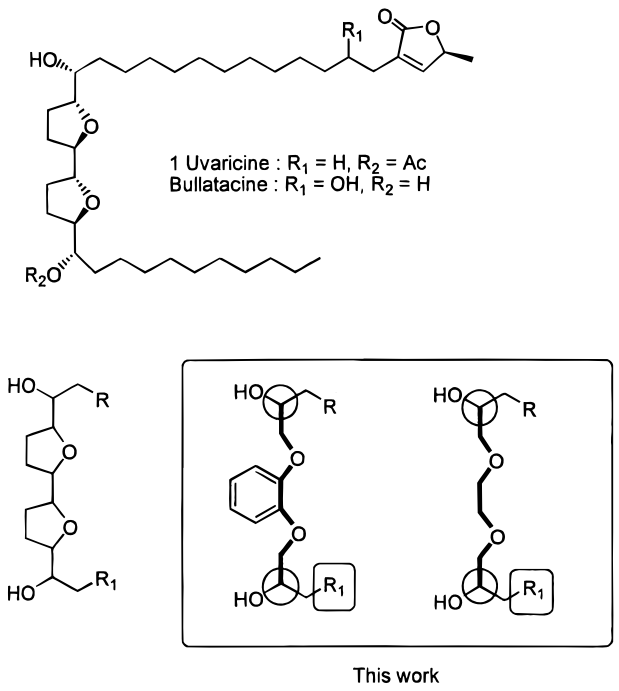

Figure 1. Simplification strategy for the synthesis of acetogenin analogues.

natural systems, this point can be critical for the biological activity, especially with respect to the selectivity. The third and final dimension to be realized was the ability to introduce a great variety of substituents in the southern fragment. Limited studies[7b,16] have shown that a shortening of this chain results in diminished activity, but no further modifications have been explored so far. In this paper, we describe the stereocontrolled synthesis in both enantiomeric forms of the precursors to simplified acetogenin analogues consisting of glycol and catechol ethers and bearing natural and modified southern chains.

Strategy. The realization of these objectives entails the following requirements: (1) The central part must be readily accessible from both glycols and catechols. (2) The absolute and relative configuration of the two hydroxyl groups must be perfectly controlled and introduced at will into any configuration. (3) The introduction of the southern end (Figure 1) must be done from a common intermediate. (4) An alkyne function must be present at the northern end to allow a coupling to a lactone- bearing synthon.

Retrosynthetically (Scheme 1), the most obvious way to introduce the northern and southern fragments was through the opening of an epoxide. These reactions are well documented for a variety of nucleophiles including those we have chosen (alkynes, alkyls, aryls, amines, and alcohols). However, the introduction of the upper and lower fragments requires that the accepting groups (the epoxides) be introduced or revealed sequentially to avoid regioselectivity and chemoselectivity issues to surface at the coupling stage. The next issue to be considered was the requirement for complete control and ready access to any desired diastereoisomer. The latent element of symmetry (either σ or C_2) was therefore the key issue to

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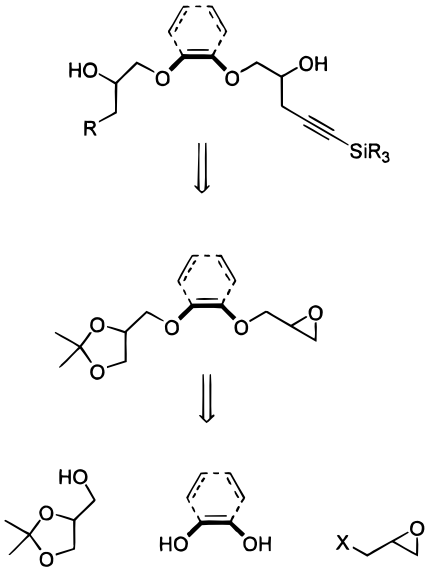
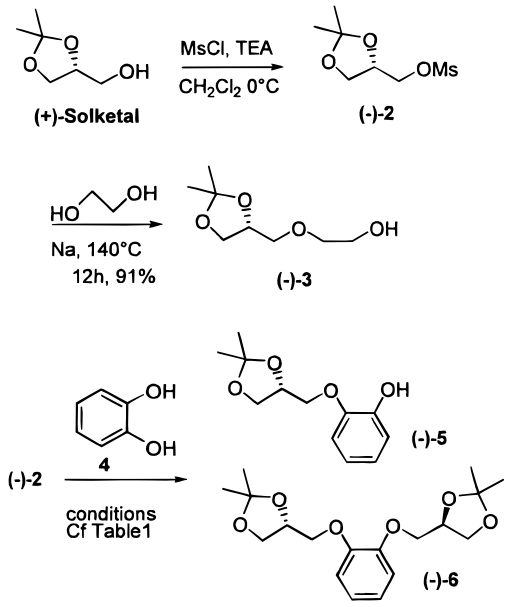
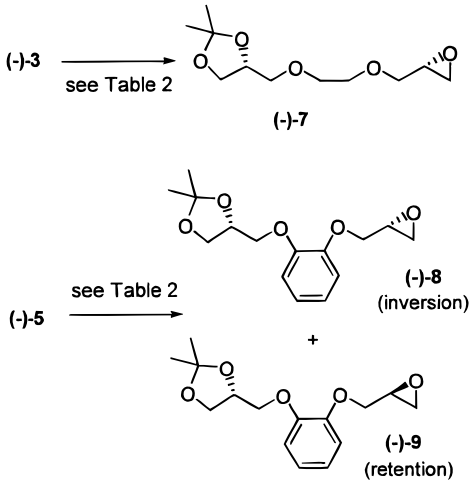
Scheme 1



Scheme 2



Scheme 3



be dealt with. We felt that an early desymmetrization of the glycol or catechol with an orthogonally masked epoxide followed by the introduction of an epoxide or epoxide precursor was the most practical approach in terms of stereochemical control and chemoselectivity. Among the epoxide precursors, diols, alkenes, and aldehydes are the most obvious, through epoxidation for the alkene, selective activation for the diol, and sulfonium chemistry for the latter. Since the Sharpless epoxidation methodology produces only low ee or de on allyl ether,[17] we chose to have the stereochemistry of the diol already set up in the reagent during the alkylation. Solketal, which is readily available in both enantiomeric forms,[18a] was selected as the masked epoxide and an activated glycidyl ether as the second partner. This approach turned out to be quite successful.

Results and Discussion

Solketal was first activated as its mesylate[18b,c] and then treated with sodium ethyleneglycoxide at 140 °C for 12 h to produce very cleanly the monoalkylated glycol (−)-**3** in 91% yield. No bis-alkylation product could be detected. In contrast, the reaction of catechol in the presence of NaH in THF led to the complete recovery of the starting mesylate. The less reactive catechol yielded itself to alkylation only after 24 h at 100 °C in DMF with NaH as the base. In this case, 10% of the bis alkylation product (−)-**6** and 21% of starting material are also recovered. They are easily separated from the product (−)-**5** by simple recrystallization. The use of K_2CO_3 instead of NaH gave a greater proportion of the bis-alkylated product with the same overall yield (Scheme 2).

With this first alkylation achieved, we turned to the introduction of the glycidyl fragment. The opening of epichlorohydrin by alkoxides is a well-known industrial process used in the synthesis of fatty glycidyl ethers.[19] This chemistry makes use of racemic epichlorohydrin, which is known to be an ambielectrophile, reacting either at the chloride- or at the epoxide-bearing centers. In the former case, the result is a retention of configuration at the central carbon atom while an inversion takes place in the latter via intramolecular chloride displacement by the alkoxide generated.[20]

Treatment of glycidyl ether (−)-**3** with optically pure epichlorohydrin under phase-transfer conditions (Scheme 3)[21,19] produced compound (−)-**7** in 78% yield with no detectable amount of a second diastereomer. At this point, the regioselectivity and therefore the relative stereochemistry of this epoxide could not be established unambiguously. They were, however, clearly demonstrated later on in the synthesis through MPA-ester analysis (vide infra). Again, the reactivity of the phenol proved quite different from the parent alkyl (−)-**5**. Under the same conditions, a 7:3 mixture of diastereomers **(8/9)** was obtained corresponding to inversion and retention

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Table 1. Alkylation of Catechol with 2 under Various Conditions

equiv of **4**	base (equiv)	solvent	*T* (°C)	time (h)	% **2**	% **5**	% **6**
2	NaH (2)	THF	20	12	100		
2	K_2CO_3 (2)	DMF	100	24	10	52	32
0.7	NaH (0.75)	DMF	100	24	10	62	21

Table 2. Alkylation of Monosubstituted Catechol with Glycidyl Chloride and Tosylate

entry	conditions[a]	reagent	reactant	products, ratio (%yield)
1	A		**3**	**7** (78)
2	A		**5**	**8**/**9**, 70/30 (80)
3	B		**5**	**8**, (86)

[a] Key: (A) 50% NaOH/hexane, TBABr, 40 °C, 12 h; (B) NaH, DMF, rt.

of configuration, respectively, at the central carbon atom. Similar results have been observed by McLure[22] under slightly different conditions. Following McLure's conditions and switching to the antipodal tosylate, we could achieve a clean alkylation to produce (−)-**8** in 80% yield with complete retention of the glycidyl configuration instead of inversion as in the case of **3** (Table 2). The enantiomers (+)-**7** and (+)-**8** were readily prepared from the corresponding reagent's enantiomers. Having in hand these bifunctional compounds, the stage was set for the introduction of the northern and southern chains. Although we could introduce at will either chain at this stage and produce both enantiomers depending on the order of addition, we could appreciate the gain in convergency that would result by introducing the alkyne first while working with two enantiomeric series instead of just one, the greater diversity being introduced at the later stages of the sequence.

Epoxide opening by acetylides or trialkylsilylacetylides in the presence of Lewis acids[23] such as $BF_3{\cdot}Et_2O$[24] or Me_3Ga[25] is a well-precedented reaction. After some optimization of the relative stoichiometries of the reagents, conditions were found to generate 70−80% yield of the desired silyl-protected homopropargylic alcohol **10** and **11**. Deprotection of the acetonide proceeded uneventfully. Selective tosylation at the primary position of the triol was realized *via* the dibutylstannylene acetal[26] in 90% yield in both series to give **12** and **13**. We had expected that the coupling of the various chain might be realized[27] at this stage of the synthesis. Unfortunately, only complex mixtures were obtained under all the conditions examined, with the notable exception of amines for which the reaction worked well. We resorted

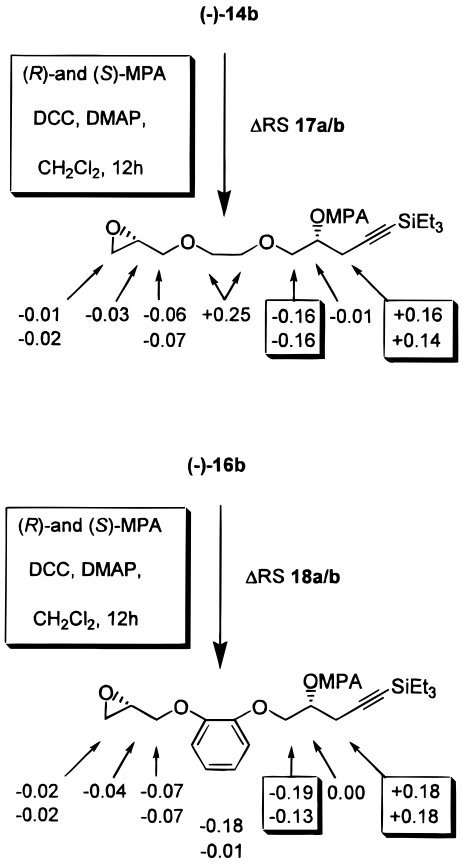

Figure 2. Determination of the absolute and relative stereochemistries of the epoxide via their MPA esters. ^1H NMR shift differences.

to generate the epoxide whose reactivity was expected to be more predictable. We then attempted the formation of the epoxide by treatment of the tosylate **12** in methanolic K_2CO_3 at 0 °C, only to find, as we should have feared, a mixture of protected **14a** and deprotected **15** epoxides (1:1). The sanction of this ratio taught us that although rapid, this deprotection was not as kinetically favored as epoxide formation since the epoxide was always present. In light of this kinetic edge, we reasoned that a more robust protecting group might better survive the conditions. Thus, the sequence was repeated with triethylsilyl-protected acetylene and under the same conditions, a 90% yield of the epoxide was realized with no trace of cleavage. Care must however be exercized in maintaining the temperature low to avoid methanol addition onto the epoxide (Scheme 4). The sequence was similarly applied in the catechol series to give **16**.

As noted earlier, although we could perform the second alkylation with complete stereoselectivity, we still required a firmly grounded confirmation. Suitable crystallinity for X-ray analysis could not be realized with the various derivatives prepared, and recourse was made to MPA-esters.[28] These esters were preferred over the more traditional MTPA (Mosher esters) for the greater Δppm and better reliability. The results for the two series are shown in Figure 2 and are in full agreement with the stereochemistry represented.

Coupling of the Epoxides 14 and 16 with Various Nucleophiles. We now had in hand multigram quanti-

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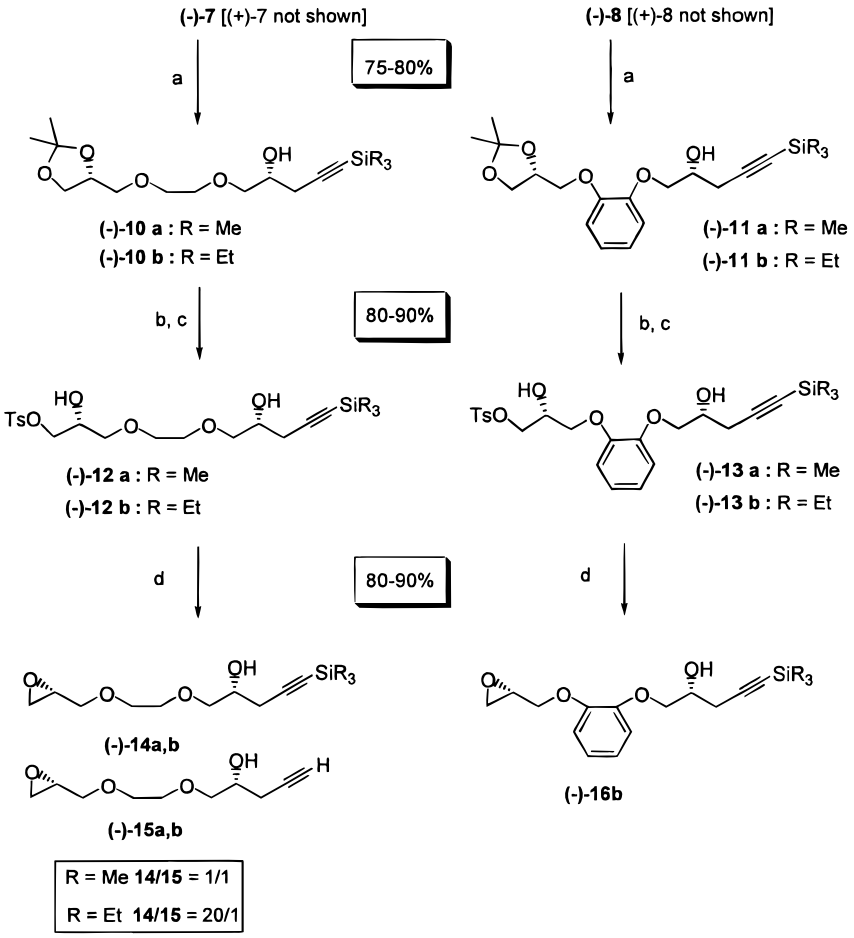
(28) (a) Latypov, S. K.; Seco, J. M.; Quiñoa, E.; Riguera, R. *J. Org. Chem.* **1996**, *61*, 8569. (b) Duret. P; Waechter, A.-I.; Figadère, B.; Hocquemiller, R.; Cavé, A. *J. Org. Chem.* **1998**, *63*, 4717.

Scheme 4[a]

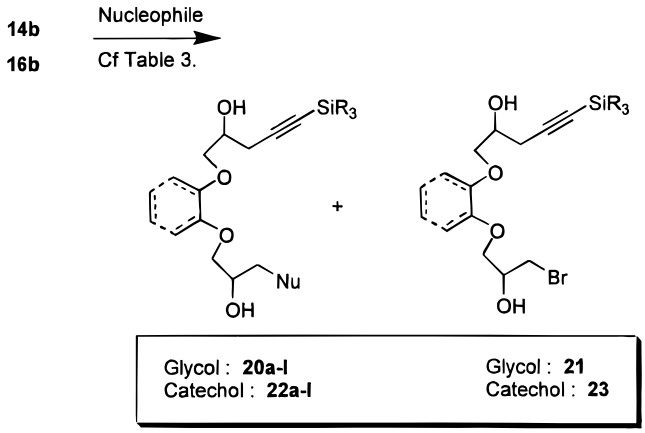


[a] Key: (a) $HCCSiR_3$, BuLi, $BF_3{\cdot}Et_2O$, THF, −78 °C; (b) *p*-TsOH, MeOH, 0 °C; (c) $Bu_2Sn(OMe)_2$, toluene, heat, then 0 °C, TsCl; (d) K_2CO_3, MeOH, 0 °C.

ties of two simplified bis-THF surrogates in both enantiomeric forms and were ready for the introduction of the southern fragments. The series of substituents was selected on the basis of the known membrane affinity of the acetogenins; starting from the natural C_9 normal alkyl chain present in the natural product, we introduced various aryl groups bearing an electron-withdrawing group (CF_3), an electron-donating group (*p*-MeO), or unsubstituted (Ph, 2-Nph). While keeping a lipophilic character they should be susceptible to engage further polar or electrostatic interactions. Next, a series of secondary amines was introduced that are expected to increase the chelating strength of the central part yet to remain liposoluble. Finally, a cholesteryl appendage was grafted.

The reaction of the Grignard reagents in the presence of copper(I) salts proceeded cleanly in the great majority of the cases with yields in the 70−85% range (Table 3, and Scheme 5). In a few instances (entries 12 and 14), along with the expected product, variable amounts of the bromohydrin were also produced. The copolarity of the two products thwarted chromatographic separation, and despite numerous experiments we were unable to pinpoint the parameters on which to act to suppress its occurrence. Resort was made to a chemical separation: the amine derivatives being part of our targets, we reasoned that these side products could be put to a useful contribution. Treatment of the mixture of product and the bromohydrin with piperidine in methanol at 40 °C for 12 h resulted in complete conversion of the side product into the now easily separable amino alcohol with no adverse effect on the other product.

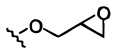
Scheme 5



The introduction of various secondary amines was uneventfully realized[29] in near-quantitative yield producing compounds of very high purity. Unsaturated or

(29) (a) Seki, T.; Takezaki, T.; Ohuchi, R.; Ohuyabi, H.; Ishimori, T.; Yasuda, K. *Chem. Pharm. Bull.* **1994**, *42*, 1609. (b) Press, J. B.; Falitico, R.; Hajos, Z. G.; Sawyers, R. A.; Kanojia, R. M.; Williams, L.; Haertlein, B.; Kauffan, J. A.; Lakas-Weiss, C.; Salata, J. J. *J. Med. Chem.* **1992**, *35*, 4509.

Table 3. Reaction of Various Nucleophiles with Epoxides 14 and 16

entry		nucleophile	conditions	products (yield, %)
1	(+)-**14b**	$C_9H_{19}MgBr$	CuBr·MS, THF, 0 °C, 1 h	(+)-**20a** (74)
2	(−)-**14b**			(−)-**20a** (71)
3	(+)-**16b**			(+)−**22a** (70)
4	(−)-**16b**			(−)-**22a** (64)
5	(+)-**14b**	PhMgBr	CuBr·MS, THF, 0 °C, 3 h	(+)-**20b** (86)
6	(−)-**14b**			(−)-**20b** (71)
7	(+)-**16b**		CuBr·MS, THF, 0 °C, 1 h	(+)-**22b** (85)
8	(−)-**16b**			(−)-**22b** (86)
9	(+)-**14b**	*p*-MeO(C_6H_4)-MgBr	CuBr·MS, THF, 0 °C, 12 h	(+)-**20c** (76)
10	(−)-**14b**			(−)-**20c** (71)
11	(−)-**16b**			(−)-**22c** (77)
12	(−)-**14b**	*p*-CF_3(C_6H_4)-MgBr	CuBr·MS, THF, 0 °C, 2 h	(−)-**20d** (25−80), (−)-**21** (0−70)
13	(−)-**16b**			(−)-**22d** (80)
14	(+)-**14b**	2-NphMgBr	CuBr·MS, THF, 0 °C, 1 h	(+)−**20e** (71), (+)−**21** (15)
15	(−)-**14b**			(−)-**20e** (80)
16	(−)-**16b**			(+)-**22e**[a] (78)
17	(+)-**14b**	piperidine	MeOH, 40 °C	(+)-**20f** (98)
18	(−)-**14b**			(−)-**20f** (98)
19	(−)-**16b**			(−)-**22f** (97)
20	(+)−**14b**	Bu_2NH	MeOH, 40 °C	(+)-**20g** (96)
21	(−)-**14b**			(−)-**20g** (97)
22	(−)-**16b**			(−)-**22g** (97)
23	(−)-**14b**	Oct_2NH	MeOH, 20 °C	(−)-**20h** (86)
24	(−)-**16b**			(−)-**22h** (87)
25	(+)-**16b**			(+)-**22h** (90)
26	*rac*-**14b**	uracil	K_2CO_3, MeOH, heat	*rac*-**20i** (0)
27	*rac*-**14b**	indole		*rac*-**20j** (0)
28	(−)-**14b**	cholesterol	BF_3·Et_2O, CH_2Cl_2, rt	(−)-**20k** (36)
29	(+)-**14b**			(−)-**20k′**[a]
30	(−)-**16b**			(−)-**22k** (38)

[a] In all cases, except these two, the sign of the optical totation is the same for product and starting material.

deactivated amines (entries 27 and 28) could, however, not be introduced under these conditions. The opening of epoxide by alcohols under Lewis acid catalysis is a well-documented reaction and usually produces good yields of the hydroxyethers. In our hands, these methods failed to provide the expected products. We suspect that a combination of intra- and intermolecular homocoupling leading to various oligomers and macrocyclized products is responsible for the low yields observed; the oxygen-rich neighboring region is probably templating the Lewis acid-catalyzed process. We turned to the method described by Bittmann,[30] which proved the most satisfactory. The desired ethers were thus obtained albeit in moderate to low yields.

(30) (a) Guivildasky, P. N.; Bittmann, R. *J. Am. Chem. Soc.* **1989**, *111*, 3077. (b) Guivildasky, P. N.; Bittmann, R. *J. Org. Chem.* **1989**, *54*, 4643.

Conclusions

In this paper, we have described a general strategy for the synthesis of a family of simplified acetogenin analogues. We have concentrated on the design of bis-ether mimicks of the central THF rings present in the natural products, consisting of ethylene glycol and catechol ethers. Starting from solketal, we have established a seven-step sequence giving access to the key epoxides **14b** and **16b** with complete stereocontrol in 35% and 26% yield, respectively. These two epoxides have been efficiently coupled to a series of alkyls, aryls, amines, and alcohols to produce a panel of 28 acetogenin precursor analogues.

The first part of this study disclosed herein constitutes the first attempt toward a comprehensive mapping of the structure−activity relationship of the acetogenins, with an emphasis on the simplification of the synthetically challenging central bis-THF part. Further studies are in progress for the synthesis of fully functionalized analogues and of southern chain analogues in the natural bis-THF series as well. These and the relevant biological data will be reported in due course.

We hope that, once completed, these studies will shed a new light on the biological activity and the therapeutic potential of this class of compounds.

Experimental Section

General Procedures. All dry solvents were freshly distilled under nitrogen from the recommended drying agent. Toluene and methanol were distilled from sodium, ether, DME and THF were distilled from sodium benzophenenone ketyl, dichloromethane was distilled from CaH_2, and triethylamine was distilled from KOH. DMF was dried over 4A MS and then distilled under reduced pressure. Other reagents and solvents were used as received from the commercial suppliers. All reactions were performed with dry solvents and under a dry argon or nitrogen atmosphere unless specified. External bath temperatures are reported. Melting points are uncorrected. FTIR was recorded on NaCl plates as thin films or as KBr pellets, specific rotation was measured at 20 °C in 1 mL quartz microcells, and the concentration is expressed in g/dL. Elemental analyses were done at the Service de Microanalyse de Gif-sur-Yvette (ICSN). MS were performed by Centre Régional de Mesures Physiques de l'Ouest. ^1H, ^{13}C, and ^{19}F NMR spectra were recorded in the specified solvent.

(4*R*)-5,6-Isopropylidene-3-oxa-1,5,6-trihydroxyhexanol ((−)-3) and (4*S*)-5,6-Isopropylidene-3-oxa-1,5,6-trihydroxyhexanol ((+)-3). Sodium (650 mg, 28.2 mmol) was carefully added to freshly distilled ethylene glycol (30 mL) at room temperature under argon atmosphere. After complete dissolution of the sodium, the solution was cooled to 0 °C, and the mesylate (−)-**2** was added dropwise. The reaction was stirred for 12 h at 140 °C, cooled, and quenched with saturated aqueous NH_4Cl. The aqueous phase was extracted with CH_2Cl_2, and the combined organic phases were washed with brine, dried ($MgSO_4$), and evaporated to yield 3.98 g (91%) of (−)-**3** as a colorless oil: FTIR (film) 3525, 1257, 1214, 1126, 1056 cm^{-1}; $[\alpha]^{20}_D$ −6.5 (*c* 3.7, $CHCl_3$); ^1H NMR ($CDCl_3$, 400 MHz) δ 4.34−4.26 (m, 1H), 4.06 (dd, 1H, J = 8.3, 6.5 Hz), 3.73 (dd, 1H, J = 8.3, 6.4 Hz), 3.75−3.72 (m, 2H), 3.64−3.59 (m, 2H), 3.57 (dd, 1H, J = 10.2, 6.0 Hz), 3.54 (dd, 1H, J = 10.2, 5.0 Hz), 2.99 (t, 1H, J = 5.7 Hz), 1.43 (s, 3H), 1.36 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 109.5, 74.8, 72.9, 72.2, 66.5, 61.6, 26.7, 25.3; HRMS (EI) for $C_7H_{13}O_4$ ($M - CH_3$)$^+$ calcd 161.0814, found 161.0813.

The (4*S*)-5,6-isopropylidene-3-oxa-1,5,6-trihydroxyhexanol ((+)-3) was prepared analogously from (+)-**2** and also gave satisfactory analytical results: $[\alpha]^{20}_D$ +6 (*c* 2.2, $CHCl_3$).

1-[(2*S*)-2,3-Dihydroxy-2,3-isopropylidenepropoxy]-2-hydroxybenzene ((−)-5) and 1-[(2*R*)-2,3-Dihydroxy-2,3-isopropylidenepropoxy]-2-hydroxybenzene ((+)-5). To a washed suspension of NaH (504 mg, 21 mmol) in 70 mL of anhydrous DMF at room temperature was added dropwise catechol (2.2 g, 20 mmol) in 15 mL of DMF. The solution was stirred for 30 min at the same temperature, and (−)-**2** (5.9 g, 28 mmol) in 15 mL of DMF was added dropwise. The reaction mixture was then stirred for 24 h at 110 °C, cooled, and quenched with 50 mL of saturated aqueous NH_4Cl. The organic layer was separated, and the aqueous phase was extracted with ether (3 × 50 mL). The combined organic phases were extracted with 10% NaOH aqueous solution, and the combined aqueous phases were neutralized with a 10% HCl aqueous solution. The aqueous phase was then extracted with ether, and the combined organic phases washed with brine, dried ($MgSO_4$), and evaporated. After recrystallization (ether/hexane), 2.75 g (62%) of (−)-**5** was isolated as colorless crystals: mp 48 °C; FTIR (film) 3450, 1597, 1520, 1250, 1155, 1111, 973, 786 cm^{-1}; $[\alpha]^{20}_D$ +2 (*c* 5.0, $CHCl_3$); ^1H NMR ($CDCl_3$, 400 MHz) δ 6.97−6.79 (m, 4H), 6.38 (bs, 1H), 4.52−4.44 (m, 1H), 4.15 (dd, 1H, *J* = 8.6, 6.6 Hz), 4.08 (dd, 1H, *J* = 10.7, 4.6 Hz), 4.03 (dd, 1H, *J* = 10.2, 5.6 Hz), 3.89 (dd, 1H, *J* = 8.1, 5.6 Hz), 1.47 (s, 3H), 1.49 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 146.7, 145.9, 122.8, 120.0, 115.4, 114.3, 110.0, 74.1, 71.1, 66.1, 26.6, 25.2; HRMS (EI) for $C_{12}H_{16}O_4$ (M^+) calcd 224.1049, found 224.1048.

The 1-[(2*R*)-2,3-dihydroxy-2,3-isopropylidenepropoxy]-2-hydroxybenzene ((+)-5) was prepared from (+)-**2** analogously and also gave satisfactory analytical results: $[\alpha]^{20}_D$ −2.1 (*c* 5.9, $CHCl_3$).

(2*R*,9*R*)-1,2-Epoxy-9,10-dihydroxy-4,7-dioxa-9,10-isopropylidenedecane ((−)-7) and (2*S*,9*S*)-1,2-Epoxy-9,10-dihydroxy-4,7-dioxa-9,10-isopropylidenedecane ((+)-7). To alcohol (−)-**3** (3.9 g, 22.2 mmol) were successively added at room temperature 4 g (51 mmol) of a 50% NaOH aqueous solution, tetrabutylammonium bromide (709 mg, 2.2 mmol), and 40 mL of hexane. (*R*)-(−)-epichlorohydrin (4 mL, 51.1 mmol) was then added dropwise, and the resulting suspension was stirred for 12 h at 60 °C. After cooling, the solution was diluted with 250 mL of ether, and 60 mL of water then extracted with ether. The combined organic phases were washed with brine, dried ($MgSO_4$), and evaporated to yield 4 g (78%) of (−)-**7** as a colorless oil: FTIR (film) 1255, 1214, 1140, 1105 cm^{-1}; $[\alpha]^{20}_D$ −14.4 (*c* 3.45, $CHCl_3$); ^1H NMR ($CDCl_3$, 400 MHz) δ 4.32−4.25 (m, 1H), 4.06 (dd, 1H, *J* = 8.1, 6.1 Hz), 3.79 (dd, 1H, *J* = 11.7, 2.6 Hz), 3.76−3.62 (m, 5H), 3.59 (dd, 1H, *J* = 10.2, 6.1 Hz), 3.51 (dd, 1H, *J* = 10.2, 5.6 Hz), 3.42 (dd, 1H, *J* = 11.7, 5.6 Hz), 3.19−3.13 (m, 1H), 2.79 (dd, 1H, *J* = 5.1, 5.1 Hz), 2.61 (dd, 1H, *J* = 4.6, 2.6 Hz), 1.42 (s, 3H), 1.36 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 109.3, 74.7, 72.3 71.9, 70.9, 70.6, 66.7, 50.8, 44.1, 26.8, 25.4; HRMS (EI) for $C_{10}H_{17}O_5$ $(M - CH_3)^+$ calcd 217.1076, found 217.1083.

The (2*S*,9*S*)-1,2-epoxy-9,10-dihydroxy-4,7-dioxa-9,10-isopropylidenedecane ((+)-7) was prepared analogously from (+)-**3** and (*S*)-(+)-epichlorohydrin and also gave satisfactory analytical results: $[\alpha]^{20}_D$ +16.5 (*c* 3.5, $CHCl_3$).

1-[(2*S*)-2,3-Dihydroxy-2,3-isopropylidenepropoxy]-2-[(2*R*)-2,3-epoxypropoxy]benzene ((−)-8) and 1-[(2*R*)-2,3-Dihydroxy-2,3-isopropylidenepropoxy]-2-[(2*S*)-2,3-epoxypropoxy]benzene ((+)-8). To a washed suspension of NaH (275 mg, 11 mmol) in 15 mL of anhydrous DMF was added dropwise at room temperature 2.34 g (10 mmol) of (−)-**5** in 7 mL of DMF. The solution was stirred for 30 min, and 2 g (8.8 mmol) of (*R*)-(−)-glycidyl tosylate in 7 mL of DMF was added dropwise. The reaction mixture was then stirred for 72 h at room temperature and quenched with saturated aqueous NH_4Cl. The aqueous phase was extracted with ether, and the combined organic phases were washed with a 10% NaOH aqueous solution and brine and dried ($MgSO_4$). After evaporation of the volatiles, the resulting solid was purified by silica gel chromatography (elution with 20% AcOEt in toluene) to give a white solid. This solid was recrystallized from ether/hexane to yield (−)-**8** (1.98 g, 80%) as colorless crystals: mp 38 °C; FTIR (film) 1593, 1504, 1454, 1372, 846, 749 cm^{-1}; $[\alpha]^{20}_D$ −21.1 (*c* 5.3, $CHCl_3$); ^1H NMR ($CDCl_3$, 400 MHz) δ 6.99−6.89 (m, 4H), 4.53−4.45 (m, 1H), 4.23 (dd, 1H, *J* = 11.2, 3.1 Hz), 4.17 (dd, 1H, *J* = 8.2, 6.1 Hz), 4.11 (dd, 1H, *J* = 9.7, 5.1 Hz), 4.03−3.95 (m, 3H), 3.39−3.34 (m, 1H), 2.88 (dd, 1H, *J* = 4.6, 4.6 Hz), 2.75 (dd, 1H, *J* = 5.1, 2.6 Hz), 1.47 (s, 3H), 1.40 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 148.8, 148.7, 122.0, 121.9, 115.1, 115.0, 109.6, 74.0, 70.2, 70.0, 66.9, 50.2, 44.7, 26.7, 25.4; HRMS (EI) for $C_{15}H_{20}O_5$ (M^+) calcd 280.1311, found 280.1308.

The 1-[(2*R*)-2,3-dihydroxy-2,3-isopropylidenepropoxy]-2-[(2*S*)-2,3-epoxypropoxy]benzene ((+)-8) was prepared analogously from (+)-**5** and (*S*)-(+)-glycidyl tosylate and also gave satisfactory analytical results: $[\alpha]^{20}_D$ +21.2 (*c* 3.6, $CHCl_3$).

General Procedure 1. Opening of Epoxides by Lithium (Triethylsilyl)acetylide. To a solution of (triethylsilyl)-acetylene in anhydrous THF at −78 °C under argon atmosphere was added dropwise a solution of *n*-butyllithium (1.6 M in hexane). After 30 min, freshly distilled $BF_3{\cdot}Et_2O$ was added dropwise, the solution was stirred for 15 min, and then the epoxide in THF was added slowly. The reaction mixture was then stirred for 3 h at −78 °C and quenched with saturated aqueous NH_4Cl. The aqueous phase was extracted with ether, and the combined organic phases were washed with brine and dried ($MgSO_4$) before evaporation of the volatiles. The resulting oil was purified by silica gel chromatography (elution with 5% MeOH in CH_2Cl_2) to give the corresponding (triethylsilyl)alkyne derivative.

(4*R*,11*R*)-6,9-Dioxa-11,12-isopropylidene-4,11,12-trihydroxy-1-(triethylsilyl)-dodec-1-yne ((−)-10b) and (4*S*,11*S*)-6,9-Dioxa-11,12-isopropylidene-4,11,12-trihydroxy-1-(triethylsilyl)dodec-1-yne ((+)-10b). According to general procedure 1, (TES)acetylene (3.3 mL, 18 mmol) in 6 mL of THF, *n*-BuLi (10.6 mL, 17 mmol), $BF_3{\cdot}Et_2O$ (2.3 mL, 19 mmol), epoxide (−)-**7** (2 g, 8.6 mmol) in 3 mL of THF were employed: colorless oil (76%); FTIR (film) 3382, 1239, 1122, 727 cm^{-1}; $[\alpha]^{20}_D$ −14.6 (*c* 3.45, $CHCl_3$); ^1H NMR ($CDCl_3$, 400 MHz) δ 4.32−4.25 (m, 1H), 4.06 (dd, 1H, *J* = 8.2, 6.1 Hz), 3.98−3.89 (m, 1H), 3.73 (dd, 1H, *J* = 8.1, 6.6 Hz), 3.71−3.61 (m, 5H), 3.58 (dd, 1H, *J* = 10.2, 5.6 Hz), 3.52 (dd, 1H, *J* = 10.2, 6.1 Hz), 3.49 (dd, 1H, *J* = 11.7, 6.7 Hz), 2.80 (d, 1H, *J* = 4.6 Hz), 2.53 (dd, 1H, *J* = 17.3, 6.1 Hz), 2.45 (dd, 1H, *J* = 16.8, 7.1 Hz), 1.42 (s, 3H), 1.36 (s, 3H), 0.98 (t, 9H, *J* = 8.1 Hz), 0.57 (q, 6H, *J* = 8.1 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 109.5, 103.6, 84.4, 74.7, 74.1, 72.3, 70.8, 70.7, 68.9, 66.7, 26.8, 25.4, 24.9, 7.5, 4.5; HRMS (EI) for $C_{18}H_{33}O_5Si$ $(M - CH_3)^+$ calcd 357.2097, found 357.2107.

The (4*S*,11*S*)-6,9-dioxa-11,12-isopropylidene-4,11,12-trihydroxy-1-(triethylsilyl)dodec-1-yne ((+)-10b) was prepared analogously from (+)-**7** and also gave satisfactory analytical results: $[\alpha]^{20}_D$ +16.7 (*c* 5.2, $CHCl_3$).

1-[(2*S*)-2,3-Dihydroxy-2,3-isopropylidenepropoxy]-2-[(2*R*)-2-hydroxy-5-(triethylsilyl)pent-4-ynoxy]benzene ((−)-11b) and 1-[(2*R*)-2,3-dihydroxy-2,3-isopropylidenepropoxy]-2-[(2*S*)-2-hydroxy-5-(triethylsilyl)pent-4-ynoxy]benzene ((+)-11b). According to general procedure 1, (TES)-acetylene (1.7 mL, 9.5 mmol) in 3 mL of THF, *n*-BuLi (6.3 mL, 10.1 mmol), $BF_3{\cdot}Et_2O$ (0.89 mL, 7.2 mmol), and epoxide (−)-**7** (1.67 g, 6 mmol) in 1 mL of THF were employed: colorless oil (78%); FTIR (film) 3473, 2174, 1594, 1503, 845, 738 cm^{-1}; $[\alpha]^{20}_D$ −32.2 (*c* 4.7, $CHCl_3$); ^1H NMR ($CHCl_3$, 400 MHz) δ 6.96−6.91 (m, 4H), 4.52−4.46 (m, 1H), 4.20 (dd, 1H, *J* = 9.5, 3.7 Hz), 4.14 (dd, 1H, *J* = 8.2, 6.4 Hz), 4.16−4.12 (m, 1H), 4.05−4.02 (m, 2H), 4.00 (dd, 1H, *J* = 9.5, 6.7 Hz), 3.95 (dd, 1H, *J* = 8.2, 5.5 Hz), 3.29 (d, 1H, *J* = 4.9 Hz), 2.66 (dd, 1H, *J* = 17.1, 5.5 Hz), 2.57 (dd, 1H, *J* = 16.8, 7.6 Hz), 1.47 (s, 3H), 1.39 (s, 3H), 0.97 (t, 9H, *J* = 8.1 Hz), 0.57 (q, 6H, *J* = 8.1 Hz); ^{13}C NMR ($CHCl_3$, 100 MHz) δ 148.89, 148.86, 122.1, 122.0, 115.2, 115.0, 109.8, 103.3, 84.6, 74.1, 72.8, 70.3, 68.5, 66.5, 26.6, 25.2, 24.7, 7.5, 4.4; HRMS (EI) for $C_{23}H_{36}O_5Si$ (M^+) calcd 420.2332, found 420.2317.

The 1-[(2*R*)-2,3-dihydroxy-2,3-isopropylidenepropoxy]-2-[(2*S*)-2-hydroxy-5-(triethylsilyl)pent-4-ynoxy]benzene ((+)-11b) was prepared analogously from (+)-**8** and also gave satisfactory analytical results: $[\alpha]^{20}_D$ +31.3 (*c* 4.5, $CHCl_3$).

General Procedure 2. Deprotection of Diols. To a solution of the acetonide in 100 mL of MeOH at room temperature was added *p*-$TsOH{\cdot}H_2O$. The reaction mixture

was stirred for 12 h at the same temperature, triethylamine was added, the volatiles were removed under vacuo, and the resulting oil was purified by silica gel chromatography (elution with 5% MeOH in AcOEt) to give the corresponding deprotected derivative.

(4*R*,11*S*)-6,9-Dioxa-4,11,12-trihydroxy-1-(triethylsilyl)-dodec-1-yne and (4*S*,11*R*)-6,9-Dioxa-4,11,12-trihydroxy-1-(triethylsilyl)dodec-1-yne. According to general procedure 2, acetonide (−)-**10b** (3 g, 8 mmol), TsOH, H_2O (150 mg, 0.8 mmol), and triethylamine (5 mL) were employed: colorless oil (86%); FTIR (film) 3382, 2173, 1122, 1047, 727 cm^{-1}; $[\alpha]^{20}_D$ −12.9 (*c* 4.3, $CHCl_3$); ^1H NMR ($CDCl_3$, 400 MHz) δ 3.99−3.91 (m, 1H), 3.91−3.84 (m, 1H), 3.79 (d, 1H, J = 4.8 Hz), 3.72−3.59 (m, 8H), 3.61 (dd, 1H, J = 9.9, 4.0 Hz), 3.58 (dd, 1H, J = 10.1, 6.4 Hz), 3.51 (dd, 1H, J = 9.9, 7.0 Hz), 3.17 (d, 1H, J = 6 Hz), 2.53 (dd, 1H, J = 16.8, 5.6 Hz), 2.44 (dd, 1H, J = 16.9, 7.6 Hz) 0.97 (t, 9H, J = 8.1 Hz), 0.58 (q, 6H, J = 8.1 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 103.6, 84.3, 74.2, 72.9, 70.6, 70.54, 70.51, 68.9, 63.8, 24.8, 7.4, 4.3; HRMS (FAB) for $C_{16}H_{33}O_5Si$ $(M + H)^+$ calcd 333.2097, found 333.2088.

The (4*S*,11*R*)-6,9-dioxa-4,11,12-trihydroxy-1-(triethylsilyl)dodec-1-yne was prepared analogously from (+)-**10b** and also gave satisfactory analytical results: $[\alpha]^{20}_D$ +12.3 (*c* 2.95, $CHCl_3$).

1-[(2*S*)-2,3-Dihydroxypropoxy]-2-[(2*R*)-2-hydroxy-5-(triethylsilyl)pent-4-ynoxy]benzene and 1-[(2*R*)-2,3-dihydroxypropoxy]-2-[(2*S*)-2-hydroxy-5-(triethylsilyl)pent-4-ynoxy]benzene. According to general procedure 2, acetonide (−)-**11b** (3.3 g, 7.85 mmol), TsOH, H_2O (150 mg, 0.8 mmol), and triethylamine (5 mL) were employed: colorless oil (90%); FTIR (film) 3453, 2174, 1594, 1503, 1125, 1033, 738 cm^{-1}; $[\alpha]^{20}_D$ −27.5 (*c* 4.55, $CHCl_3$); ^1H NMR ($CDCl_3$, 400 MHz) δ 6.98−6.88 (m, 4H), 4.22 (dd, 1H, J = 9.1, 2.5 Hz), 4.18−4.10 (m, 2H), 4.08−4.00 (m, 4H), 3.98 (dd, 1H, J = 9.1, 7.6 Hz), 3.85−3.73 (m, 2H), 3.32 (t, 1H, J = 5.1 Hz), 2.63 (dd, 1H, J = 16.8, 5.6 Hz), 2.54 (dd, 1H, J = 16.8, 8.1 Hz), 0.97 (t, 9H, J = 8.1 Hz), 0.57 (q, 6H, J = 8.1 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 148.8, 148.5, 122.4, 122.1, 115.4, 114.6, 103.1, 84.8 72.7, 72.4, 70.1, 68.6, 63.9, 24.7, 7.4, 4.3; HRMS (EI) for $C_{20}H_{32}O_5Si$ (M^+) calcd 380.2019, found 380.2004.

The 1-[(2*R*)-2,3-dihydroxypropoxy]-2-[(2*S*)-2-hydroxy-5-(triethylsilyl)pent-4-ynoxy]benzene was prepared analogously from (+)-**11b** and also gave satisfactory analytical results: $[\alpha]^{20}_D$ +23.5 (*c* 4.85, $CHCl_3$).

General Procedure 3. Selective Primary Tosylation. (Dibutyl)tin(dimethoxide) was added to the triol in anhydrous toluene at room temperature, and half of the solvent was distilled. The reaction mixture was cooled to −15 °C, and triethylamine and *p*-toluenesulfonyl chloride were successively added before the solution was allowed to reach room temperature. The reaction mixture was stirred for 17 h and quenched with water, and the aqueous phase was extracted with ether. The combined organic phases were washed with brine and dried ($MgSO_4$), and the volatiles were removed under vacuo. The resulting oil was purified by silica gel chromatography (elution with CH_2Cl_2 then 5% MeOH in CH_2Cl_2) to give the corresponding tosylated derivative.

(4*R*,11*R*)-6,9-Dioxa-12-(*p*-toluenesulfonyl)-4,11,12-trihydroxy-1-(triethylsilyl)dodec-1-yne ((−)-12b) and (4*S*,11*S*)-6,9-Dioxa-12-(*p*-toluenesulfonyl)-4,11,12-trihydroxy-1-(triethylsilyl)dodec-1-yne ((+)-12b). According to general procedure 3, the triol was obtained from (−)-**10b** (1.16 g, 4 mmol) in 150 mL of toluene, (dibutyl)tin(dimethoxide) (1 mL, 4.4 mmol), triethylamine (0.03 mL), and *p*-toluenesulfonyl chloride (991 mg, 5.2 mmol): colorless oil (88%); FTIR (film) 3422, 2173, 1189, 1097, 1018, 815 cm^{-1}; $[\alpha]^{20}_D$ −7.8 (*c* 3.65, $CHCl_3$); ^1H NMR ($CDCl_3$, 400 MHz) δ 7.79 (d, 2H, J = 8.2 Hz), 7.35 (d, 2H, J = 8.2 Hz), 4.09−3.96 (m, 3H), 3.95−3.87 (m, 1H), 3.66−3.59 (m, 5H), 3.56 (dd, 1H, J = 10.1, 4.0 Hz), 3.51 (dd, 1H, J = 10.1, 5.6 Hz), 3.47 (dd, 1H, J = 10.0, 7.1 Hz), 3.26 (d, 1H, J = 5.4 Hz), 2.98 (d, 1H, J = 4.6 Hz), 2.50 (dd, 1H, J = 16.8, 5.7 Hz), 2.45 (s, 3H), 2.42 (dd, 1H, J = 16.8, 7.2 Hz), 0.97 (t, 9H, J = 8.1 Hz), 0.57 (q, 6H, J = 8.1 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 144.9, 132.5, 129.8, 127.9, 103.4, 84.4, 74.0, 71.4, 70.6, 70.5, 70.3, 68.8, 68.1, 24.8, 21.6, 7.4, 4.4; HRMS (FAB) for $C_{23}H_{39}O_7SSi$ $(M + H)^+$ calcd 487.2186, found 487.2186.

The (4*S*,11*S*)-6,9-dioxa-12-(*p*-toluenesulfonyl)-4,11,12-trihydroxy-1-(triethylsilyl)dodec-1-yne ((+)-12b) was prepared analogously from the triol obtained from (+)-**10b** and also gave satisfactory analytical results: $[\alpha]^{20}$ +7.5 (*c* 3.05, $CHCl_3$)

1-[(2*R*)-2,3-Dihydroxy-3-(*p*-toluenesulfonyl)propoxy]-2-[(2*R*)-2-hydroxy-5-(triethylsilyl)pent-4-ynoxy]benzene ((−)-13b) and 1-[(2*S*)-2,3-dihydroxy-3-(*p*-toluenesulfonyl)propoxy]-2-[(2*S*)-2-hydroxy-5-(triethylsilyl)pent-4-ynoxy]benzene ((+)-13b). According to general procedure 3, the triol was obtained from (−)-**11b** (2.8 g, 7.4 mmol) in 250 mL of toluene, (dibutyl)tin(dimethoxide) (1.77 mL, 7.7 mmol), triethylamine (0.06 mL), and *p*-toluenesulfonyl chloride (2 g, 10.3 mmol): colorless oil (91%); FTIR (film) 3422, 2173, 1595, 1503, 1125, 1019, 831, 738 cm^{-1}; $[\alpha]^{20}_D$ −15.6 (*c* 6.3, $CHCl_3$); ^1H NMR ($CDCl_3$, 400 MHz) δ 7.78 (d, 2H, J = 8.2 Hz), 7.31 (d, 2H, J = 8.2 Hz), 6.99−6.85 (m, 4H), 4.21−4.08 (m, 5H), 4.04 (dd, 1H, J = 9.8, 3.4 Hz), 4.00−3.94 (m, 2H), 3.60 (d, 1H, J = 4.4 Hz), 3.27 (d, 1H, J = 4.2 Hz), 2.60 (dd, 1H, J = 16.9, 5.6 Hz), 2.52 (dd, 1H, J = 16.9, 7.5 Hz), 2.42 (s, 3H), 0.97 (t, 9H, J = 8.1 Hz), 0.57 (q, 6H, J = 8.1 Hz). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 148.9, 148.6, 145.1, 132.4, 129.9, 127.9, 122.7, 122.4, 115.9, 115.6, 102.9, 84.9, 72.9, 70.5, 69.9, 68.6, 67.9, 24.8, 21.6, 7.4, 4.3; HRMS (EI) for $C_{27}H_{38}O_7SSi$ (M^+) calcd 534.2107, found 534.2106.

The 1-[(2*S*)-2,3-dihydroxy-3-(*p*-toluenesulfonyl)propoxy]-2-[(2*S*)-2-hydroxy-5-(triethylsilyl)pent-4-ynoxy]benzene ((+)-13b) was prepared analogously from the triol obtained from (+)-**11b** and also gave satisfactory analytical results: $[\alpha]^{20}_D$ +15.9 (*c* 4.6, $CHCl_3$).

General Procedure 4. Formation of Epoxides. To a solution of the tosylate in $MeOH/CH_2Cl_2$ 10/1 at 0 °C was added K_2CO_3. The suspension was stirred for 1 h at the same temperature, and the volatiles were removed in vacuo. The resulting white paste was dissolved in CH_2Cl_2, washed with water, dried ($MgSO_4$), and after evaporation purified by silica gel chromatography (elution with 5% MeOH in CH_2Cl_2) to give the corresponding epoxy derivative.

(4*R*,11*S*)-6,9-Dioxa-11,12-epoxy-4-hydroxy-1-(triethylsilyl)dodec-1-yne ((−)-14b) and (4*S*,11*R*)-6,9-Dioxa-11,12-epoxy-4-hydroxy-1-(triethylsilyl)dodec-1-yne ((+)-14b). According to general procedure 4, tosylate (−)-**12b** (750 mg, 1.5 mmol) in 5 mL of MeOH and 0.5 mL of CH_2Cl_2, and K_2CO_3 (470 mg, 3.4 mmol) were employed: colorless oil (87%); FTIR (film) 3442, 2173, 1105, 1017 cm^{-1}; $[\alpha]^{20}_D$ −11 (*c* 3.3, $CHCl_3$); ^1H NMR ($CDCl_3$, 400 MHz) δ 3.99−3.90 (m, 1H), 3.82 (dd, 1H, J = 11.7, 3.0 Hz), 3.74−3.63 (m, 5H), 3.51 (dd, 1H, J = 9.6, 7.1 Hz), 3.43 (dd, 1H, J = 11.2, 5.6 Hz), 3.20−3.13 (m, 1H), 2.80 (t, 1H, J = 4.6 Hz), 2.73 (d, 1H, J = 4.6 Hz), 2.62 (dd, 1H, 4.6, 2.6 Hz), 2.53 (dd, 1H, J = 16.8, 5.6 Hz), 2.46 (dd, 1H, J = 16.8, 7.6 Hz), 0.97 (t, 9H, J = 8.1 Hz), 0.57 (q, 6H, J = 8.1 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 103.6, 84.5, 74.1, 71.9, 70.8, 70.6, 68.8, 50.8, 44.2, 24.8, 7.4, 4.4; HRMS (EI) for $C_{16}H_{31}O_4Si$ $(M + H)^+$ calcd 315.1992, found 315.1995. Anal. Calcd for $C_{16}H_{30}O_4Si$: C, 61.11; H, 9.61. Found: C, 60.53; H, 9.61.

The (4*S*,11*R*)-6,9-dioxa-11,12-epoxy-4-hydroxy-1-(triethylsilyl)dodec-1-yne ((+)-14) was prepared analogously from (+)-**12b** and also gave satisfactory analytical results: $[\alpha]^{20}_D$ +10 (*c* 3.0, $CHCl_3$).

1-[(2*S*)-2,3-Epoxypropoxy]-2-[(2*R*)-2-hydroxy-5-(triethylsilyl)pent-4-ynoxy]benzene ((−)-16b) and 1-[(2*R*)-2,3-Epoxypropoxy]-2-[(2*R*)-2-hydroxy-5-(triethylsilyl)pent-4-ynoxy]benzene ((+)-16b). According to general procedure 4, tosylate (−)-**13b** (1.84 mg, 3.4 mmol) in 25 mL of MeOH, 2.5 mL of CH_2Cl_2, and K_2CO_3 (1 g, 7.5 mmol) were employed: colorless oil (89%); FTIR (film) 3442, 2173, 1594, 1503, 1019, 738 cm^{-1}; $[\alpha]^{20}_D$ −20.4 (*c* 5.1, $CHCl_3$); ^1H NMR ($CDCl_3$, 400 MHz) δ 6.99−6.93 (m, 4H), 4.29 (dd, 1H, J = 11.2, 3.0 Hz), 4.21 (dd, 1H, J = 9.2, 3.1 Hz), 4.18−4.11 (m, 1H), 4.02 (dd, 1H, J = 9.2, 6.6 Hz), 3.95 (dd, 1H, J = 11.7, 6.1 Hz), 3.41−3.35 (m, 1H), 3.24 (d, 1H, J = 4.6 Hz), 2.92−2.89 (m, 1H), 3.76

(dd, 1H, J = 4.6, 2.5 Hz), 2.67 (dd, 1H, J = 17.3, 5.6 Hz), 2.58 (dd, 1H, J = 16.8, 7.1 Hz), 0.97 (t, 9H, J = 8.1 Hz), 0.58 (q, 6H, J = 8.1 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 149.0, 148.7, 122.5, 122.0, 115.7, 115.3, 103.3, 84.7, 72.8, 70.7, 68.4, 50.4, 44.6, 24.7, 7.4, 4.3; HRMS for $C_{20}H_{30}O_4Si$ (M^+) calcd 362.1913, found 362.1926.

The 1-[(2*R*)-2,3-epoxypropoxy]-2-[(2*R*)-2-hydroxy-5-(triethylsilyl)pent-4-ynoxy]benzene ((+)-16b) was prepared analogously from (+)-**13b** and also gave satisfactory analytical results: $[\alpha]^{20}_D$ +19.8 (*c* 4.65, $CHCl_3$).

General Procedure 5. Methoxymandelic Esters Synthesis. To the alcohol in 1 mL of anhydrous CH_2Cl_2 at room temperature were successively added methoxymandelic acid, DCC, and DMAP. The solution was strirred for 12 h at room temperature and then filtrated. The filtrate after concentration was purified by silica gel chromatography (elution with 50% ether in hexane) to give the corresponding mandelic ester.

(*4R,11R*)-6,9-Dioxa-11,12-epoxy-4-hydroxy-4-O−((2*R*)-2-methoxy-2-phenylacetate)-1-(triethylsilyl)-dodec-1-yne ((−)-17a). According to general procedure 5, alcohol (−)-**14b** (20 mg, 0.064 mmol), (*R*)-(−)-MPA (17 mg, 0.1 mmol), DCC (29 mg, 0.14 mmol), and DMAP (4 mg, 0.032 mmol) were employed: colorless oil (61%); FTIR (film) 2361, 2177, 1762, 1111, 729 cm^{-1}; $[\alpha]^{20}_D$ −38.5 (*c* 7.5, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.47−7.43 (m, 2H), 7.38−7.31 (m, 3H), 5.16−5.10 (m, 1H), 4.78 (s, 1H), 3.70 (dd, 1H, J = 11.6, 2.9 Hz), 3.54 (d, 2H, J = 5 Hz), 3.50−3.30 (m, 4H), 3.42 (s, 3H), 3.35 (dd, 1H, J = 11.6, 5.8 Hz), 3.14−3.09 (m, 1H), 2.78 (dd, 1H, J = 5.1, 4.2 Hz), 2.65 (dd, 1H, J = 17.2, 6.6 Hz), 2.59 (dd, 1H, J = 5.0, 2.7 Hz), 2.57 (dd, 1H, J = 17.1, 5.9 Hz), 0.98 (t, 9H, J = 7.8 Hz), 0.57 (q, 6H, J = 7.8 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 170.2, 136.1, 128.7, 128.5, 127.2, 102.3, 84.5, 82.4, 71.8, 71.6, 70.8, 70.7, 70.5, 57.3, 50.8, 44.2, 22.1, 7.4, 4.4; HRMS (EI) for $C_{25}H_{38}O_6Si$ (M^+) calcd 462.2438, found 462.2438.

(4*R*,11*R*)-6,9-Dioxa-11,12-epoxy-4-hydroxy-4-*O*-[(2*S*)-2-methoxy-2-phenylacetate]-1-(triethylsilyl)dodec-1-yne ((−)-17b). According to general procedure 5, alcohol (−)-**14b** (20 mg, 0.064 mmol), (*S*)-(+)-MPA (17 mg, 0.1 mmol), DCC (29 mg, 0.14 mmol), and DMAP (4 mg, 0.032 mmol) were employed: Colorless oil (64%); FTIR (film) 2177, 1762, 1111, 729 cm^{-1}; $[\alpha]^{20}_D$ +10.6 (*c* 7.5, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.47−7.43 (m, 2H), 7.38−7.31 (m, 3H), 5.18−5.11 (m, 1H), 4.79 (s, 1H), 3.77 (dd, 1H, J = 11.6, 2.9 Hz), 3.70 (m, 2H), 3.67−3.55 (m, 4H), 3.43 (s, 3H), 3.41 (dd, 1H, J = 11.8, 6.0 Hz), 3.17−3.12 (m, 1H), 2.79 (dd, 1H, J = 4.9, 4.1 Hz), 2.61 (dd, 1H, J = 5.0, 2.7 Hz), 2.49 (dd, 1H, J = 17.1, 7.0 Hz), 2.43 (dd, 1H, J = 16.9, 5.3 Hz), 0.95 (t, 9H, J = 7.8 Hz), 0.53 (q, 6H, J = 7.8 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 170.2, 136.0, 128.7, 128.6, 127.1, 102.1, 84.5, 82.5, 71.9, 71.4, 70.82, 70.78, 70.6, 57.4, 50.8, 44.2, 21.9, 7.4, 4.3; HRMS (EI) for $C_{25}H_{38}O_6Si$ (M^+) calcd 462.2438, found 462.2441.

1-[(2*S*)-2,3-Epoxypropoxy]-2-[(2*R*)-2-hydroxy-2-*O*-[(2*R*)-2-methoxy-2-phenylacetate]-5-(triethylsilyl)pent-4-ynoxy]-benzene ((−)-18a). According to general procedure 5, alcohol (−)-**16b** (37 mg, 0.1 mmol), (*R*)-(−)-MPA (27 mg, 0.16 mmol), DCC (45 mg, 0.22 mmol), and DMAP (8 mg, 0.05 mmol) were employed: colorless oil (63%); FTIR (film) 2361, 2177, 1753, 1502, 1115, 736 cm^{-1}; $[\alpha]^{20}_D$ −36.0 (*c* 7.5, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.46−7.44 (m, 2H), 7.34−7.27 (m, 3H), 6.96−6.84 (m, 3H), 6.77−6.72 (m, 1H), 5.37−5.30 (m, 1H), 4.81 (s, 1H), 4.14 (dd, 1H, J = 11.2, 3.3 Hz), 4.10 (m, 2H), 3.92 (dd, 1H, J = 11.2, 5.4 Hz), 3.43 (s, 3H) 3.31−3.27 (m, 1H), 2.85 (dd, 1H, J = 5.0, 4.2 Hz), 2.82 (dd, 1H, J = 17.1, 6.8 Hz), 2.73 (dd, 1H, J = 17.1, 5.7 Hz), 2.72 (dd, 1H, J = 5.0, 2.7 Hz), 0.96 (t, 9H, J = 7.8 Hz), 0.56 (q, 6H, J = 7.8 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 170.2, 148.71, 148.69, 136.0, 128.7, 128.6, 127.1, 122.1, 122.0, 115.5, 115.0, 101.9, 84.9, 82.4, 71.0, 70.2, 68.8, 57.4, 50.2, 44.7, 22.2, 7.4, 4.3; HRMS(EI) for $C_{29}H_{38}O_6Si$ (M^+) calcd 510.2438, found 510.2446.

1-[(2*S*)-2,3-Epoxypropoxy]-2-[(2*R*)-2-hydroxy-2-*O*-[(2*S*)-2-methoxy-2-phenylacetate)-5-(triethylsilyl)pent-4-ynoxy]-benzene ((−)-18b). According to general procedure 5, alcohol (−)-**16b** (30 mg, 0.083 mmol), (*S*)-(+)-MPA (22 mg, 0.135 mmol), DCC (38 mg, 0.18 mmol), and DMAP (5 mg, 0.04 mmol) were employed: colorless oil (64%); FTIR (film) 2361, 2177, 1753, 1502, 1115, 736 cm^{-1}; $[\alpha]^{20}_D$ +11 (*c* 7.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.45−7.41 (m, 2H), 7.36−7.30 (m, 3H), 6.96−6.89 (m, 4H), 5.37−5.31 (m, 1H), 4.77 (s, 1H), 4.29 (dd, 1H, J = 10.8, 3.9 Hz), 4.23 (dd, 1H, J = 10.7, 5.8 Hz)-), 4.21 (dd, 1H, J = 11.2, 3.3 Hz), 3.99 (dd, 1H, J = 11.2, 5.5 Hz), 3.41 (s, 3H), 3.35−3.31 (m, 1H), 2.87 (dd, 1H, J = 5.0, 4.2 Hz), 2.74 (dd, 1H, J = 5.0, 2.6 Hz), 2.64 (dd, 1H, J = 17.0, 7.3 Hz), 2.55 (dd, 1H, J = 17.0, 5.3 Hz), 0.92 (t, 9H, J = 7.8 Hz), 0.52 (q, 6H, J = 7.8 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 170.1, 148.9, 148.8, 135.9, 128.7, 128.6, 127.1, 122.2, 122.1, 115.7, 115.1, 101.7, 84.9, 82.3), 71.1, 70.3, 68.9, 57.4, 50.2, 44.7, 21.9, 7.4, 4.3; HRMS (EI) for $C_{29}H_{38}O_6Si$ (M^+) calcd 510.2438, found 510.2446.

General Procedure 6. Opening of Epoxides with Grignard Reagent. A 1 M solution of the Grignard in anhydrous THF or ether was added dropwise to a suspension of CuBr·Me_2S in THF at 0 °C under an argon atmosphere. The solution was then stirred for 10 min, and the epoxide in THF was added dropwise. The reaction mixture was stirred for a range of 1−12 h at 0 °C and then quenched with saturated aqueous NH_4Cl. The aqueous phase was extracted with ether, and the combined organic phases were washed with brine and dried ($MgSO_4$) before evaporation of the volatiles. The resulting oil was purified by silica gel chromatography (elution with 2% MeOH in CH_2Cl_2) to give the corresponding open derivative.

General Procedure 7. Opening of Epoxides with Secondary Amines. To the amine in anhydrous MeOH at room temperature was added dropwise the epoxide in MeOH. The solution was stirred for 12 h at 40 °C, and the solvent and excess amine were removed under vacuo to give the corresponding amino derivative.

General Procedure 8. Opening of Epoxides with Cholesterol. To cholesterol and the epoxide in anhydrous CH_2Cl_2 at room temperature was added BF_3·Et_2O. The suspension was stirred for 72 h at room temperature, and the solvent was evaporated. The resulting white paste was purified by silica gel chromatography (elution 5% MeOH in CH_2Cl_2) to give the corresponding cholesteryl derivative.

Acknowledgment. This research was supported by Laboratoires Servier, the CNRS, and the Ministère de l'Education Supérieure et de la Recherche. Y.L.H. thanks Laboratoire Servier and Drs. Renard and Pfeiffer for a graduate fellowship. We thanks Profs. Gesson and Figadère for fruitful discussions. In addition, we thank Pierre Guenot for recording the mass spectra.

Supporting Information Available: ^{1}H and ^{13}C NMR spectra of all compounds described and characterization for compounds **20a**−**k** and **22a**−**k**. This material is available free of charge via the Internet at http://pubs.acs.org.

JO990772H