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Synthesis of a Benzolactone Collection using Click Chemistry

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A collection of benzotriazoles consisting of seven compounds was prepared from the propynyl-substituted benzolactone **1** and various azides using click chemistry. The lactone **1** was obtained through a short route by direct esterification of the allylbenzoic acid **9** with the alkynol **7** giving the benzoate **2**. The homopropargyl alcohol **7** in turn was obtained by opening the epoxide **6** with triisopropylsilyl acetylide. Ring-closing metathesis of the ester **2** using Grubbs catalyst II followed by removal of the silicon protecting group furnished the lactone **1**. Two of the benzotriazoles, **17a** and **17b**, were also converted into the corresponding phenols to probe the role of the phenolic OH on the biological activity. All nine benzotriazoles showed cytotoxic activity in a L929 mouse fibroblast assay with IC_{50} values in the low micromolar range.

Introduction

One goal of chemical genetics is to find a selective small molecule inhibitor for the most important proteins.[1] This should be achieved by populating the corresponding chemical space in a well-balanced manner.[2] In a brute force approach large numbers of small molecules would be required, which however might pose enormous technological and financial challenges. In order to increase the hit rate and to populate the complementary biological space, recourse has been taken to natural product libraries which have shown some promising results. For example, a library based on the carpanone core structure led to the discovery of compounds that inhibit vesicular trafficking. Thus, while carpanone itself is devoid of useful biological activity,[3] the analog CLL-19 obtained from a combinatorial synthesis campaign turned out to inhibit exocytosis from Golgi (Figure 1).[4]

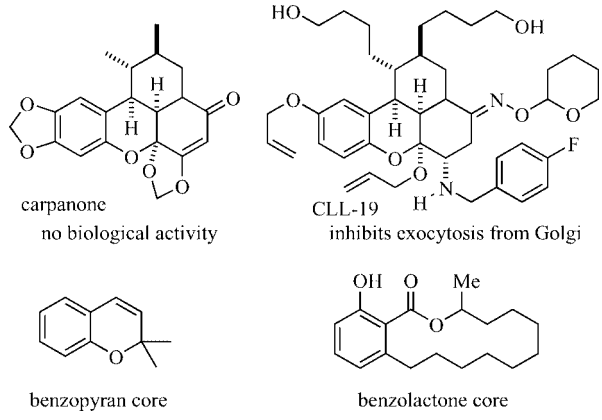

Figure 1. A natural product library based on carpanone and two priveledged core structures.

Many other natural product-like libraries which are known are based on so-called privileged structures. This term refers to molecular subunits, that are associated with a high degree of biological activity across more than one biological target. Representative examples include benzopyrans and benzolactones (Figure 1). One might argue that privileged structures are a consequence of the biosynthetic machinery, meaning they are available by well-established pathways, such as polyketide or terpene biosynthesis. One very prominent structural motif among the polyketides is the benzolactone core. Several representative examples are shown in Figure 2. Frequently, they have a 14-membered macrolactone ring with various degree of functionalization. Common to the 14-membered benzolactones is the acetate starter unit resulting in a methyl side chain. Zearalenone is a fungal metabolite with oestrogenic activity.[5] Radicicol has antifungal and antibiotic properties which are due to inhibition of the HSP90.[6] The lactone LL-783,277 turned out to be a MEK inhibitor,[7] whereas aigialomycin blocks cyclin dependent kinases.[8] While it seems that these benzolactones have a propensity for protein kinases, there is a selectivity for individual kinase targets.

The ring size in benzolactones may vary. For example in several benzolactone enamides, the lactone ring is smaller but the side chain is longer and functionalized. Salicylihalamide A, apicularen A and oximidine II are typical examples

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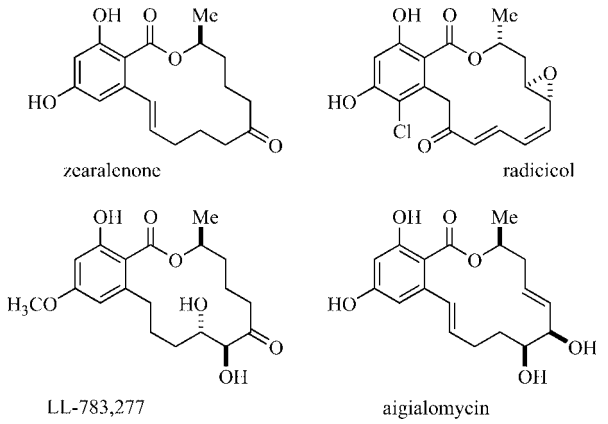


Figure 2. Typical 14-membered benzolactones with a methyl substituent.

for benzolactone enamides (Figure 3).[9] The enamide side chain is essential for the biological activity, which is due to inhibition of V-ATPase, a membrane bound proton pump.[10] The functionalized side chain inspired us to design simplified benzolactones that would carry different residues in this region. The idea was to possibly generate novel dual mode binding natural product analogs. For this purpose a suitable, easily accessible benzolactone core was required together with a functional group in the side chain that has a high diversity potential. In this regard a propynyl side chain seemed ideal since with the terminal alkyne many different conjugation reactions seem to be possible. Thus, Sonogashira couplings or Reppe–Vollhardt reactions are ideal methods. Another very powerful method for performing ligation-type reactions on terminal alkynes is the Cu^{I}-catalyzed 1,3-dipolar cycloaddition reaction yielding difunctionalized triazoles.[11–13] This reaction has found use

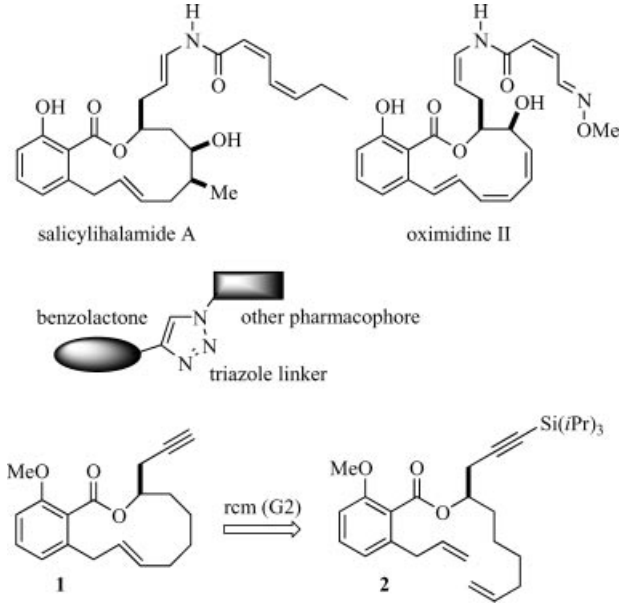


Figure 3. Design of dual domain benzolactone analogs utilizing click chemistry on alkyne **1**.

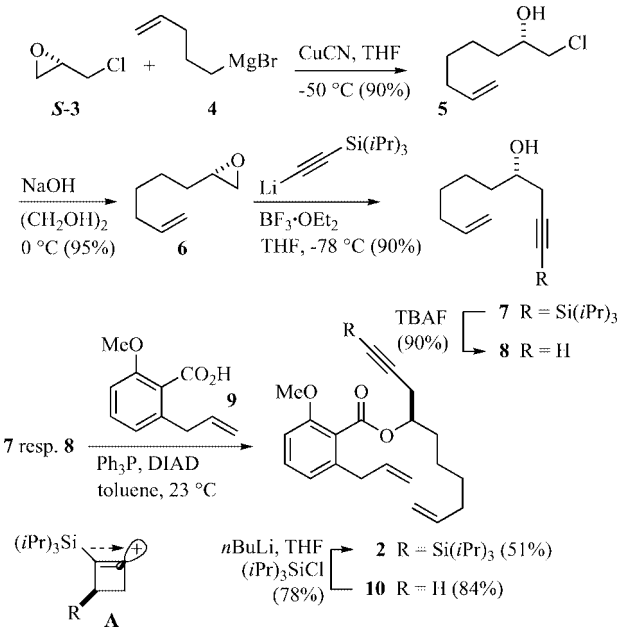
in drug discovery,[14] chemical biology,[15,16] and other fields.[17] As the macrolactone core we chose the simplified salicylihalimide compound **1**. This selection was based on the facile construction of the salicylihalamide core by a ring-closing metathesis reaction of a suitable ester having a double bond at both termini. In a previous paper we illustrated the synthesis of lactone **1** from the propynyl-6-heptenyl benzoate **2**.[18] However, in order for the ring-closing metathesis reaction with the second generation Grubbs catalyst to succeed, the triple bond required protection with a bulky triisopropylsilyl group.

In this paper we illustrate a shorter synthesis of the benzoate **2** and also the derivatization of the triple bond of the lactone **1** by Cu^{I}-catalyzed 1,3-dipolar cycloaddition reactions with several azides.

Results

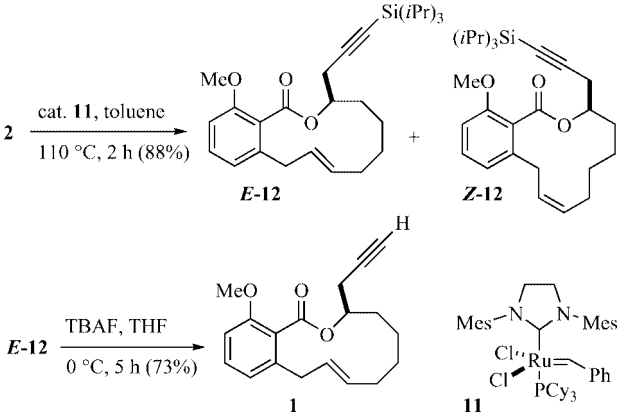
Synthesis

As described previously,[18] opening of (*S*)-epichlorohydrin[19] (**3**) with 4-pentenylmagnesium bromide (**4**) in presence of copper cyanide led to the chlorohydrin **5** in 90% yield (Scheme 1). Epoxide formation under basic conditions provided the (*S*)-oxirane **6** in almost quantitative yield as a colorless oil. In the next step the epoxide **6** was opened with the lithium anion of triisopropylacetylene in the presence of boron trifluoride–diethyl ether resulting in the chiral secondary alcohol **7**. This reaction worked quite well and gave a much higher yield than the corresponding opening with lithium trimethylsilylacetylide. Esterification of the homopropargyl alcohol **7** with the 2-allylbenzoic acid **9** had to be performed under Mitsunobu conditions in order to reach the salicylihalamide configuration. While in related cases this reaction works quite well, in the present situation it required optimized conditions in order to give a reasonable yield. Reliable result were obtained with recrystallized (from MeOH) triphenylphosphane and diisopropyl diazodicarboxylate (DIAD) in toluene as solvent. In contrast, the Mitsunobu esterification of the alcohol **8**, obtained from the TIPS-alkynol **7** by treatment with tetrabutylammonium fluoride, gave the corresponding ester in 84% yield.[18] While we have not further investigated the reason for this difference one might speculate that the intermediate oxaphosphonium salt is attacked intramolecularly by the triple bond leading to a cylobutenyl cation, stabilized by hyperconjugation from the C–Si bond as indicated with structure **A** (Scheme 1). Alternatively, a cyclopropane may form. In both cases, reaction of the cation with a nucleophile (water etc.) could produce the corresponding ketone. Somewhat related cases from the literature support this hypothesis.[20] In comparison, deprotonation of the alkyne **10** with *n*BuLi followed by trapping of the anion with triisopropylsilyl chloride provided the benzoate **2** in 78% yield.[18] Nevertheless, the direct condensation of alkynol **7** with acid[21] **9** still was the best option.



Scheme 1. Synthesis of the benzoate **2** via Mitsunobu esterification of acid **9** with alkynol **7**.

The crucial ring-closing metathesis of **2** was performed in refluxing toluene (1.1 mM) using the Grubbs catalyst **11** (0.05 equiv.) (Scheme 2). The two isomers ***E*-12** and ***Z*-12** could be separated by flash chromatography. They were formed in an *E*/*Z*-ratio of 6:1. Recrystallization of the *E* isomer from EtOH gave crystals suitable for X-ray analysis. A rendering of this structure is shown in Figure 4. One can clearly see the bent shape of the macrolactone and the orientation of the carboxyl group more or less orthogonal to the aromatic ring. Finally, treatment of the macrolactone ***E*-12** with tetrabutylammonium fluoride (TBAF) in THF induced cleavage of the carbon–silicon bond with liberation of the terminal alkyne **1**.



Scheme 2. Ring-closing metathesis of benzoate **2** using Grubbs catalyst II (**11**).

The idea in this project was to connect the privileged benzolactone fragment by click chemistry to other subunits in order to see whether the new conjugates can be steered to other dual domain binding sites. For this purpose a small collection of azides was prepared according to known

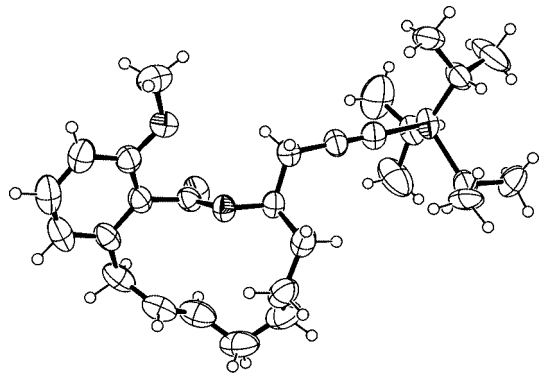
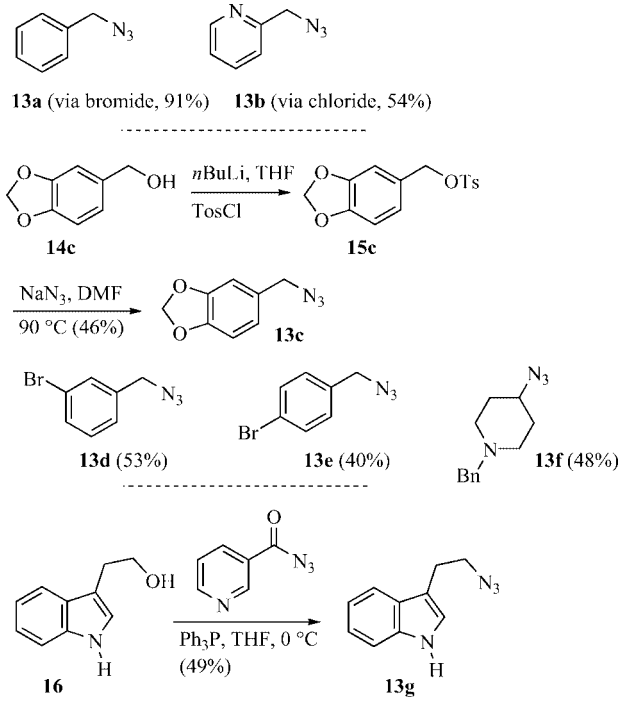


Figure 4. X-ray structure of macrolactone ***E*-12**.

methods. The azide **13a** was obtained from the bromide,[22] whereas for the azide **13b** the chloride served as starting material.[23] For the azides **13c–f** the two-step procedure via the corresponding tosylate followed by S_N2 substitution with sodium azide in DMF, turned out to be more reliable.[24] A third method is based on the reaction of an alcohol with nicotinoyl azide under Mitsunobu conditions (Ph_3P, DEAD).[25] Using this method the azide **13g** (Scheme 3) was prepared from 2-(1*H*-indol-3-yl)ethanol (**16**).

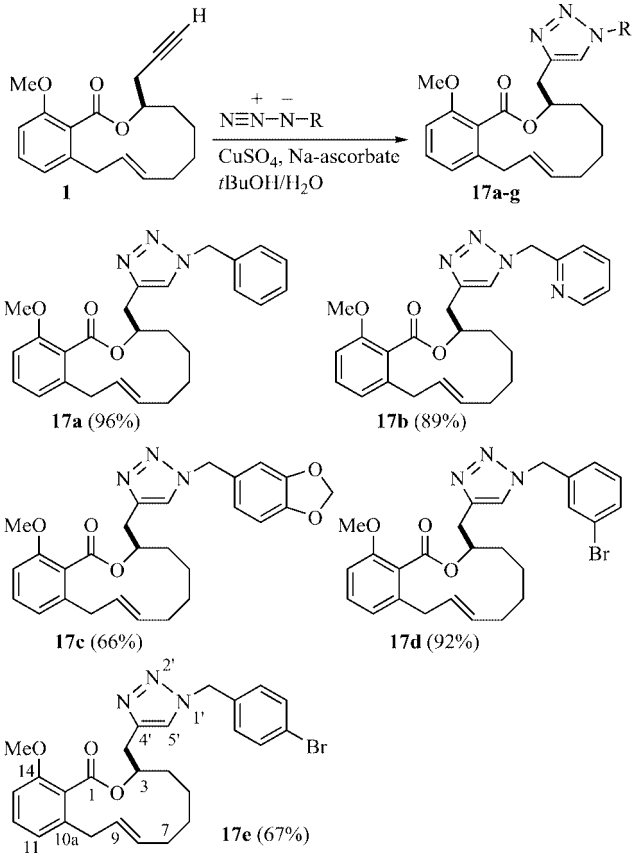


Scheme 3. Synthesis of the azides **13a–g** by S_N2 reactions.

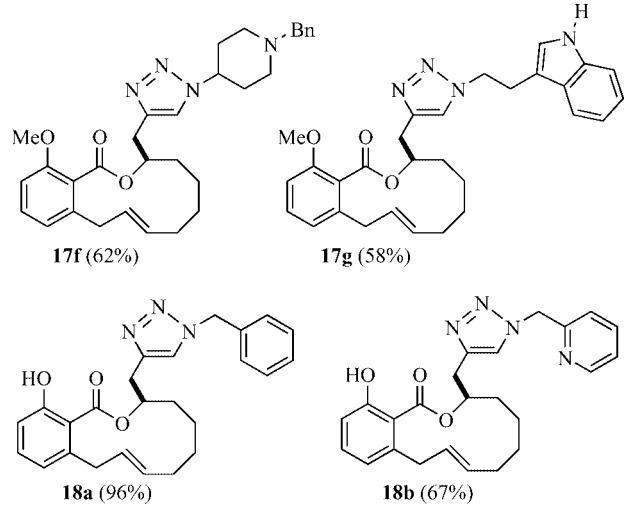
With the azide **13a–g** in hand, the 1,3-dipolar cycloaddition reaction of the alkyne **1** leading to the triazoles **17a–g** could be investigated. Accordingly, using conditions put forward by Sharpless et al.,[12a,26] a solution of the alkyne **1** (1 equiv.) and an azide (1.2–1.4 equiv.) in degassed ethanol was treated with a copper(II) sulfate solution (1.18 equiv.) and a sodium ascorbate solution (1.5 equiv.) as reducing agent. In general, the Cu^I-catalyzed 1,3-dipolar cycload-

dition was complete within 20 h at room temperature. As can be seen in Scheme 4, a range of benzylic azides reacted smoothly under these conditions. The reaction is also compatible with a pyridine ring (cf. structure **17b**) and aryl bromides (cf. structures **17d** and **17e**).

Further examples that successfully could be obtained, include the piperidine derivative **17f** and the indole derivative **17g** (Scheme 5). In order to check for the role of the methoxy group as compared to a hydroxy group, the two compounds **17a** and **17b** were treated with 9-I-9-BBN in CH_2Cl_2 for a short time resulting in the hydroxylactones **18a** (96%) and **18b** (67%), respectively. The aromatic proton of the triazole typically appears at around 7.40–7.60 ppm in $CDCl_3$ as solvent. The two carbon atoms in the triazole ring resonate at around δ = 122 (C-5′) and δ = 144 (C-4′) ppm.



Scheme 4. Synthesis of the triazoles **17a**–**e** using the corresponding benzylic azides and lactone **1**.



Scheme 5. Synthesis of the triazoles **17f** and **17g** from lactone **1**. Cleavage of the aromatic methyl ether to give the lactone-triazole conjugates **18a** and **18b**.

Biological Studies

The biological activity of the compounds were tested by a growth inhibition assay with fibroblast cells of the mouse cell line L929 (ACC2, DSMZ). The cells were cultivated in Dulbeco's modified Eagle medium with high glucose and 10% fetal calf serum at 37 °C and 10% CO_2. Aliquots of 120 µL of suspended cells (50,000 mL^{-1}) were given to 60 µL of serial dilutions of the compounds in 96-well microplates. After 5 d the reduction of MTT (3-[4,5-dimethylthiazol-2-yl]-2,5-diphenyltetrazolium bromide) was measured as a parameter of growth and metabolic activity of the cells and related to control cells that were incubated with the solvent only. The IC_{50} values obtained are given in Table 1. Among the compounds tested the triazole **17f** was the most active one (entry 6). The other compounds were almost equally active except for **17b** and **18b** which contain a pyridine moiety in the side chain and were clearly less efficacious in inhibiting cell propagation.

Table 1. Results of a cytotoxicity assay of benzotrialzoles **17a**–**17g**, **18a**, and **18b** with L929 mouse fibroblasts.

Entry	Compound	IC_{50} [µg mL^{-1}]	IC_{50} [µmol L^{-1}]
1	**17a**	6	14
2	**17b**	20	46
3	**17c**	9	19
4	**17d**	9	18
5	**17e**	7	18
6	**17f**	5	10
7	**17g**	6	12
8	**18a**	6	14
9	**18b**	20	48

The more active compounds **17a**, **17c**–**g**, **18a** were checked for special phenotypic effects with PtK_2 potoroo cells at 12 to 20 µg mL^{-1}. Cells (ATCC CCL-56) grown on glass coverslips (13 mm diameter) in four well plates were incubated with the compounds overnight, fixed with cold (–20 °C) acetone/methanol (1:1) for 10 min and labelled for endoplasmatic reticulum (ER) with a primary antibody against GRP-94 (1:1000; Affinity BioReagents) and a secondary goat *anti*-rat IgG antibody conjugated with Alexa Fluor 448 (10 µg mL^{-1}; Molecular Probes). Other cells were fixed in 4% formalin and stained with Alexa Fluor 594 phalloidin (2 U mL^{-1}; Molecular Probes) for the actin cytoskeleton.

Living cells were also stained for lysosomes with an azidotropic reagent (50 nM LysoTracker Red DND-99; Molecular Probes) at 37 °C for 30 min after they had been in-

cubated with the inhibitor for 3.5 h, and examined under the fluorescent microscope.

We did not find alteration in the ER system that are typical for V-ATPase inhibitors and no sign that the acidification of the lysosomes that is accomplished by the action of V-ATPases is inhibited. Thus, we do not assume that toxicity of the compounds is due to V-ATPase inhibition. Compared to the control, it seemed that in the treated cells the actin cortex was more rigid and distinct, pointing to an increased actin polymerization. Whether this is a direct effect of the triazoles or just a side effect has to be elucidated.

Conclusions

In this paper we describe a straightforward synthesis of the benzolactone **1** which carries a propynyl side chain. The benzolactone was designed with the polyketide-derived natural product salicylihalamide A as a lead structure. Key reactions in the synthesis of THE lactone **1** include opening of the terminal epoxide **6** with lithium triisopropylsilylacetylide giving the homopropargyl alcohol **7**. A subsequent Mitsunobu esterification of **7** with the acid **9** led to the ester **2** which served as a substrate for a ring-closing metathesis reaction. The bulky triisopropyl group protects the alkyne during the metathesis reaction. The derived benzolactone **1** was combined with several azides leading to the corresponding triazoles. Growth inhibition assay showed moderate cytotoxicity (IC_{50} down to 10 μM) for these compounds. Nevertheless, the concept of combining sophisticated priviledged structures derived from natural products with other pharmacophores by click chemistry could be of broad interest.

Experimental Section

General: ^1H and ^{13}C NMR: Bruker Avance 400 spectrometer; spectra were recorded at 295 K in $CDCl_3$; chemical shifts are calibrated to the residual proton and carbon resonance of the solvent or to added TMS: $CDCl_3$ (δ_H = 7.25, δ_C = 77.0 ppm), C_6D_6 (δ_H = 7.16, δ_C = 128.0 ppm). Melting points: Büchi Melting Point B-540, uncorrected. IR: Jasco FT/IR-430 apparatus (cm^{-1}). MS: Finnigan Triple-Stage-Quadrupole TSQ-70 (ionizing voltage of 70 eV). HRMS: Intectra AMD MAT-711A (EI) mass spectrometers. Flash chromatography: J. T. Baker silica gel, 43–60 μm. Thin-layer chromatography: Macherey–Nagel Polygram Sil G/UV254 plates. All solvents used in the reactions were distilled before use. Dry tetrahydrofuran and toluene were distilled from sodium and benzophenone, whereas dry dichloromethane was distilled from $CaCO_3$. Acetone was dried by distillation from phosphorus pentoxide. Petroleum ether with a boiling range of 40–60 °C was used. Reactions were generally run under argon. All commercially available compounds were used as received, unless stated otherwise. (2*S*)-1-Chloro-7-octen-2-ol (**5**) and (2*S*)-2-(5-hexenyl)oxirane (**6**) were prepared according to Herb et al.[18] Benzyl azide (**13a**) was prepared according to Alvarez.[22]

(4*S*)-1-(Triisopropylsilyl)-9-decen-1-yn-4-ol (7): A cooled (–78 °C) solution of (triisopropylsilyl)acetylene (5.78 g, 31.7 mmol) in THF (200 mL) was treated with *n*BuLi (19.8 mL, 31.7 mmol, 1.6 M in hexane) and the suspension was stirred for 1 h at that temperature. After addition of boron trifluoride–diethyl ether (3.90 mL, 4.36 g, 30.7 mmol) the mixture was stirred for another h and then slowly treated with a solution of the epoxide **6** (2.50 g, 19.81 mmol) in THF (60 mL). The temperature was kept for 1.5 h, and the reaction was quenched by addition of saturated NH_4Cl solution (5 mL). The mixture was poured into a saturated NH_4Cl solution (120 mL) and extracted with diethyl ether (3 × 100 mL). The combined organic extracts were washed with saturated $NaHCO_3$ solution (240 mL), brine (240 mL), and dried with $MgSO_4$. After filtration and evaporation of the solvent the crude product was purified by flash chromatography (petroleum ether/ethyl acetate, 9:1) to afford the hydroxyalkyne **7** (6.44 g, 90%) as a light yellow oil. R_f = 0.43 (petroleum ether/ethyl acetate, 9:1). $[\alpha]_D$ = +0.67 (c = 2.0, CH_2Cl_2). ^1H NMR (400 MHz, $CDCl_3$): δ = 1.01–1.05 [m, 21 H, $CH(CH_3)_2$], 1.30–1.60 (m, 6 H, CH_2), 1.99–2.07 (m, 3 H, OH, 8-H), 2.37 (dd, J = 16.7, 6.6 Hz, 1 H, 3-H), 2.48 (dd, J = 16.8, 4.9 Hz, 1 H, 3-H), 3.69–3.76 (m, 1 H, C*H*OH), 4.92 (dd, J = 10.1, 0.8 Hz, 1 H, CH=CH_2), 4.98 (dd, J = 17.1, 1.6 Hz, 1 H, CH=CH_2), 5.78 (ddt, J = 17.1, 10.2, 5.1 Hz, 1 H, C*H*=CH_2) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 11.2 [*C*H(CH_3)$_2$], 18.6 [CH(*C*H$_3$)$_2$], 25.0 (C-6), 28.8 (C-3), 28.9 (C-7), 33.6 (C-8), 36.0 (C-5), 69.9 (C-4), 83.5 (C-1), 104.7 (C-2), 114.4 (C-10), 138.8 (C-9) ppm. IR (film): $\tilde{\nu}$ = 1463, 1641, 2172, 2360, 2865, 2940, 3383 cm^{-1}. MS (EI): m/z (%) = 265 (3), 247 (18), 139 (44), 131 (86), 111 (45), 103 (100), 92 (36), 83 (50), 75 (40), 69 (22). HRMS (EI): $[M - CH_3]^+$ calcd. for $C_{16}H_{29}OSi$ 265.1988, found 265.2038.

(4*S*)-9-Decen-1-yn-4-ol (8): To a solution of the alkyne **7** (200 mg, 0.65 mmol) in THF (2 mL) was added TBAF (1.94 mL, 1.94 mmol, 1 M in THF) at 0 °C. After being stirred for 2 h at room temperature, the solution was treated with saturated aqueous $NaHCO_3$ solution (10 mL) and the mixture extracted with Et_2O (2 × 10 mL). The combined extracts were dried ($MgSO_4$), filtered, and concentrated. The residue was purified by flash chromatography (petroleum ether/ethyl acetate, 9:1) to provide the desired alkynol **8** (89 mg, 90%) as a colorless wax. R_f = 0.23 (petroleum ether/ethyl acetate, 9:1). $[\alpha]_D$ = –2.44 (c = 1.0, CH_2Cl_2). ^1H NMR (400 MHz, $CDCl_3$): δ = 1.30–1.48 (m, 4 H, 6-H, 7-H), 1.51–1.56 (m, 2 H, 5-H), 1.94 (br., 1 H, OH) 2.03–2.07 (m, 3 H, CH_2=CHCH_2, 1-H), 2.27–2.45 (m, 2 H, 3-H), 3.72–3.78 (m, 1 H, C*H*OH), 4.92–5.01 (m, 2 H, CH_2=CH), 5.74–5.84 (m, 1 H, CH_2=C*H*) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 25.0 (C-6), 27.3 (C-3), 28.7 (C-7), 33.6 (C-8), 36.0 (C-5), 69.8 (C-4), 70.8 (C-1), 80.9 (C-2), 114.5 (C-10), 138.8 (C-9) ppm.

(1*R*)-1-[3-(Triisopropylsilyl)-2-propynyl]-6-heptenyl 2-Methoxy-6-(2-propenyl)benzoate (2): To a solution of alcohol **7** (3.80 g, 12.31 mmol) and triphenylphosphane (4.84 g, 18.47 mmol, recrystallized from methanol) in toluene (45 mL) was added dropwise a solution of acid[21] **9** (6.62 g, 34.46 mmol) and diisopropyl azodicarboxylate (DIAD) (3.64 mL, 3.74 g, 18.47 mmol) in toluene (20 mL). After 1.5 h of stirring at room temperature, the solvent was removed in vacuo and the residue purified by flash chromatography (petroleum ether/ethyl acetate, 15:1). Ester **2** (3.03 g, 51%) was isolated as a colorless oil. R_f = 0.65 (petroleum ether/ethyl acetate, 9:1). $[\alpha]_D$ = +33.5 (c = 1.0, CH_2Cl_2). ^1H NMR (400 MHz, $CDCl_3$): δ = 1.01–1.05 [m, 21 H, $CH(CH_3)_2$], 1.37–1.52 (m, 4 H, CH_2), 1.73–1.97 (m, 2 H, 2′-H), 2.07 (br. dt, J = 6.3, 6.3 Hz, 2 H, 5′-H), 2.58 (dd, J = 16.8, 8.0 Hz, 1 H, 1′′-H), 2.73 (dd, J = 16.7, 4.3 Hz, 1 H, 1′′-H), 3.35 (br. d, J = 6.3 Hz, 2 H, CH_2CH=CH_2), 3.79 (s, 3 H, OCH_3), 4.93 (br. d, J = 10.1 Hz, 1 H, CH=CH_2), 5.00 (br. d, J = 17.1 Hz, 1 H, CH=CH_2), 5.05 (br. d, J = 10.4 Hz, 1 H, CH_2CH=CH_2), 5.05 (br. d, J = 17.2 Hz, 1 H, CH_2CH=CH_2), 5.13–5.20 (m, 1 H, 1′-H), 5.80 (ddt, J = 17.1, 10.1, 6.7 Hz, 1 H, C*H*=CH_2), 5.86–5.97 (m, 1 H, CH_2C*H*=CH_2), 6.77 (d, J = 8.3 Hz,

1 H, 3-H), 6.82 (d, J = 7.7 Hz, 1 H, 5-H), 7.27 (m, 1 H, 4-H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 11.2 [$CH(CH_3)_2$], 18.55 [$CH(CH_3)_2$], 24.5 (C-3′), 25.4 (C-1′′), 28.6 (C-4′), 32.8 (C-2′), 33.6 (C-5′), 37.4 ($CH_2CH{=}CH_2$), 55.8 (OCH_3), 70.5 (C-3′), 73.0 (C-1′), 83.1 (C-3′′), 103.7 (C-2′′), 108.9 (C-3), 114.5 ($CH{=}CH_2$), 116.4 ($CH_2CH{=}CH_2$), 121.6 (C-5), 123.8 (C-1), 130.3 (C-4), 136.4 ($CH_2CH{=}CH_2$), 138.3 (C-6), 138.7 (C-6′), 156.4 (C-2), 167.7 (C=O) ppm. IR (film): $\tilde{\nu}$ = 1469, 1640, 1727, 2174, 2362, 2864, 2942 cm^{-1}. MS (EI): m/z (%) = 439 (4), 306 (23), 305 (100), 175 (42), 147 (23). HRMS (EI): [M – iPr]$^+$ calcd. for $C_{27}H_{39}SiO_3$ 439.2668, found 439.2655.

14-Methoxy-3-[3-(triisopropylsilyl)-2-propynyl]-3,4,5,6,7,10-hexahydro-1*H*-2-benzoxacyclododecin-1-one (12): The Grubbs II catalyst **11** (40 mg, 0.047 mmol, 0.05 equiv.) was added under argon to a solution of the dienoate **2** (450 mg, 0.932 mmol) in toluene (850 mL). Upon addition of the catalyst the solution turned violet and after warming became golden-yellow. The mixture was refluxed for 2 h. After complete reaction (TLC control) and cooling to room temperature, the solvent was removed in vacuo. The residue was purified by flash chromatography (petroleum ether/diethyl ether, 30:1) to provide the benzolactones ***E*-12** (319 mg, 75%) and ***Z*-12** (54 mg, 13%) as colorless solids. Recrystallization of ***E*-12** from ethanol gave crystals suitable for X-ray analysis. CCDC-624498 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

***E*-12 (main product):** M.p. 104–105 °C. R_f = 0.38 (petroleum ether/diethyl ether, 15:1). $[\alpha]_D$ = –28.3 (c = 1.0, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.97–1.10 [m, 22 H, $CH(CH_3)_2$, 5-H], 1.21–1.34 (m, 1 H, 6-H), 1.44–1.55 (m, 1 H, 6-H), 1.58–1.68 (m, 2 H, 5-H, 7-H), 1.70–1.79 (m, 1 H, 1′-H), 1.81–1.91 (m,1 H, 1′-H), 2.13–2.22 (m, 1 H, 7-H), 2.53 (dd, J = 16.4, 9.4 Hz, 1 H, 4-H), 2.83 (dd, J = 16.4, 4.1 Hz, 1 H, 4-H), 3.15 (d, J = 14.3 Hz, 1 H, 10-H), 3.72 (dd, J = 14.3, 10.3 Hz, 1 H, 10-H), 3.77 (s, 3 H, OCH_3), 5.05–5.14 (m, 1 H, 3-H), 5.24–5.34 (m, 1 H, 9-H), 5.36–5.47 (m, 1 H, 8-H), 6.78 (d, J = 7.3 Hz, 1 H, 11-H), 6.78 (d, J = 8.7 Hz, 1 H, 13-H), 7.24 (m, 1 H, 12-H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 11.2 [$CH(CH_3)_2$], 18.6 [$CH(CH_3)_2$], 19.8 (C-6), 24.4 (C-5), 25.3 (C-4), 31.3 (C-1′), 32.7 (C-7), 37.8 (C-10), 55.9 (OCH_3), 70.6 (C-3), 82.9 (C-3′), 104.0 (C-2′), 109.6 (C-13), 122.4 (C-11), 124.0 (C-14a), 128.9 (C-9), 130.3 (C-12), 132.6 (C-8), 139.4 (C-10a), 156.9 (C-14), 167.8 (C-1) ppm. IR (KBr): $\tilde{\nu}$ = 1069, 1117, 1256, 1275, 1470, 1726, 2864, 2941 cm^{-1}. MS (EI): m/z (%) = 412 (34), 411 (100), 393 (8), 378 (9), 305 (33), 263 (23), 175 (31), 131 (33), 103 (51), 75 (32). HRMS (EI): [M – iPr]$^+$ calcd. for $C_{25}H_{35}SiO_3$ 411.2355, found 411.2383.

***Z*-12 (minor product):** R_f = 0.19 (petroleum ether/diethyl ether, 15:1). $[\alpha]_D$ = –3.5 (c = 1.0, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.05 [br. s, 21 H, $CH(CH_3)_2$], 1.37–1.53 (m, 4 H, 5-H, 6-H), 1.85–2.09 (m, 3 H, 1′-H, 7-H), 2.31–2.42 (m, 1 H, 7-H), 2.57–2.63 (m, 2 H, 4-H), 3.20 (br. d, J = 15.0 Hz, 1 H, 10-H), 3.51 (dd, J = 15.0, 10.2 Hz, 1 H, 10-H), 3.79 (s, 3 H, OCH_3), 5.13–5.22 (m, 1 H, 8-H), 5.29–5.36 (m, 1 H, 3-H), 5.43–5.51 (m, 1 H, 9-H), 6.75 (d, J = 8.3 Hz, 1 H, 13-H), 6.89 (d, J = 7.7 Hz, 1 H, 11-H), 7.28 (dd, J = 8.3, 7.7 Hz, 1 H, 12-H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 11.2 [$CH(CH_3)_2$], 17.8 (C-6), 18.6 [$CH(CH_3)_2$], 23.6 (C-4), 24.4 (C-7), 26.3 (C-5), 28.5 (C-1′), 31.6 (C-10), 55.8 (OCH_3), 73.3 (C-3), 82.9 (C-3′), 103.6 (C-2′), 108.6 (C-13), 121.9 (C-11), 123.9 (C-14a), 129.5 (C-8), 130.0 (C-9), 130.4 (C-12), 139.4 (C-10a), 156.2 (C-14), 167.7 (C-1) ppm.

(3*R*)-14-Methoxy-3-(2-propynyl)-3,4,5,6,7,10-hexahydro-1*H*-2-benzoxacyclododecin-1-one (1): To a solution of TIPS-alkyne ***E*-12** (487 mg, 1.071 mmol) in THF (10 mL) was added TBAF (5.4 mL, 5.4 mmol, 1 M in THF) at 0 °C. After being stirred for 5 h at room temperature, the solution was treated with saturated aqueous $NaHCO_3$ solution (10 mL) and the mixture extracted with Et_2O (2 × 15 mL). The combined extracts were dried ($MgSO_4$), filtered, and concentrated. The residue was purified by flash chromatography (petroleum ether/ethyl acetate, 15:1) to provide the desired alkyne **1** (234 mg, 73%) as a colorless wax. R_f = 0.58 (petroleum ether/ethyl acetate, 9:1). $[\alpha]_D$ = –21.9 (c = 1.0, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.97–1.05 (m, 1 H, 4-H, 5-H, 6-H), 1.16–1.26 (m, 1 H, 4-H, 5-H, 6-H), 1.37–1.47 (m, 1 H, 4-H, 5-H, 6-H), 1.51–1.64 (m, 3 H, 4-H, 5-H, 6-H), 1.72–1.81 (m, 1 H, 4-H), 1.95 (br. s, 1 H, 3′-H), 2.12–2.21 (m, 1 H, 7-H), 2.55 (d, J = 2.02 Hz, 2 H, 1′-H), 3.08 (dd, J = 14.2, 1.3 Hz, 1 H, 10-H), 3.64 (dd, J = 14.0, 10.5 Hz, 1 H, 10-H), 3.79 (s, 1 H, OCH_3), 5.07–5.14 (m, 3 H, 3-H), 5.24–5.32 (m, 1 H, 9-H), 5.35–5.45 (m, 1 H, 8-H), 6.71 (d, J = 7.0 Hz, 1 H, 11-H), 6.79 (d, J = 7.7 Hz, 1 H, 13-H), 7.23 (m, 1 H, 12-H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 19.7 (C-6), 23.9 (C-5), 24.6 (C-4), 31.4 (C-1′), 32.7 (C-7), 37.8 (C-10), 55.8 (OCH_3), 69.7 (C-3), 70.2 (C-3′), 80.1 (C-2′), 109.6 (C-13), 122.4 (C-11), 123.9 (C-14a), 128.9 (C-9), 130.3 (C-12), 132.6 (C-8), 139.4 (C-10a), 156.9 (C-14), 167.9 (C-1) ppm. IR (film): $\tilde{\nu}$ = 1069, 1118, 1278, 1470, 1584, 1723, 2864, 2939, 3291, 3547 cm^{-1}. MS (EI): m/z (%) = 298 (15), 177 (20), 131 (91), 103 (100), 75 (89), 61 (38). HRMS (EI): [M]$^+$ calcd. for $C_{19}H_{22}O_3$ 298.1569, found 298.1557.

2-(Azidomethyl)pyridine (13b): A solution of 2-(chloromethyl)pyridine hydrochloride (500 mg, 3.05 mmol) in water (18 mL) was treated with sodium azide (0.79 g, 12.1 mmol), followed by refluxing the mixture for 2 d. After cooling to room temperature, the mixture was neutrilized with solid $NaHCO_3$. The mixture was extracted with CH_2Cl_2 (3 × 20 mL). The combined organic extracts were dried with MgSO4, filtered, and concentrated in vacuo. The residue, a brown oil, was purified by flash chromatography (petroleum ether/ethyl acetate, 4:1) to yield azide **13b** as a colorless oil (220.8 mg, 54%). R_f = 0.2 (petroleum ether/ethyl acetate, 9:1).

General Procedure for the Preparation of Benzylic Tosylates 15c–f: To a solution of the alcohol in THF (0.25 M) was added nBuLi (1.6 M in hexane, 1.1 equiv.) at 0 °C. After being stirred for 15 min at 0 °C, TsCl (1.5 equiv.) was added. The resulting mixture was stirred at 70 °C for 15 h which results in the precipitation of a colorless solid. The reaction mixture was diluted with water (15 mL/mmol of alcohol) and extracted with CH_2Cl_2 (3 × 10 mL/mmol of alcohol). Drying of the organic phase with $MgSO_4$, followed by filtration and evaporation of the solvent in vacuo, gave the crude tosylate which was used for the next step without further purification.

(1,3-Benzodioxol-5-yl)methyl 4-Methylbenzenesulfonate (15c): Alcohol **14c** (200 mg, 1.31 mmol) in THF (5 mL) was converted to tosylate **13c** using nBuLi (1.6 M in hexane, 0.9 mL, 1.45 mmol) and tosyl chloride (288 mg, 1.51 mmol). R_f = 0.76 (petroleum ether/ethyl acetate, 2:1). The crude tosylate was used immediately for the subsequent substitution with sodium azide. Attempted chromatography led to decomposition of this tosylate.

(3-Bromophenyl)methyl 4-Methylbenzenesulfonate: (3-Bromophenyl)methanol (245 mg, 1.31 mmol) in THF (5 mL) was converted to tosylate **15d** using nBuLi (1.6 M in hexane, 0.9 mL, 1.45 mmol) and tosyl chloride (288 mg, 1.51 mmol). R_f = 0.80 (petroleum ether/ethyl acetate, 3:1).

(4-Bromophenyl)methyl 4-Methylbenzenesulfonate: (4-Bromophenyl)methanol (245 mg, 1.31 mmol) in THF (5 mL) was converted to tosylate **15e** using nBuLi (1.6 M in hexane, 0.9 mL,

1.45 mmol) and tosyl chloride (288 mg, 1.51 mmol). R_f = 0.80 (petroleum ether/ethyl acetate, 3:1).

1-Benzyl-4-piperidinyl 4-Methylbenzenesulfonate: 1-Benzyl-4-piperidinol (251 mg, 1.31 mmol) in THF (5 mL) was converted to tosylate **15f** using *n*BuLi (1.6 M in hexane, 0.9 mL, 1.45 mmol) and tosyl chloride (288 mg, 1.51 mmol). R_f = 0.72 (petroleum ether/ethyl acetate, 3:1).

General Procedure for the Preparation of the Azides 13c–13f: A mixture of the crude tosylate in dry DMF (0.16 M) and NaN_3 (2.6 equiv.) was stirred at 90 °C for 5 h which results in a white precipitate. The mixture was diluted with water (40 mL/mmol of tosylate) and extracted with CH_2Cl_2 (3 × 15 mL/mmol of tosylate). The combined organic extracts were dried with $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by flash chromatography to yield azides as colorless oils.

(1,3-Benzodioxol-5-yl)methyl Azide (13c): The crude tosylate **14c** (1.31 mmol) in DMF (8 mL) was converted to azide **13c** using NaN_3 (221 mg, 3.40 mmol) according to the above procedure. Purification of the crude product by flash chromatography (petroleum ether/ethyl acetate) gave 107 mg (46%) of azide **13c**. R_f = 0.91 (petroleum ether/ethyl acetate, 1:1). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.02 (s, 2 H, CH_2N_3), 5.77 (s, 2 H, OCH_2O), 6.52–6.67 (m, 3 H, aromatic H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 54.6 (CH_2), 101.2 (OCH_2O), 108.7 (C-7), 121.9 (C-6), 128.9 (C-5), 147.6 (C-3a), 148.0 (C-7a) ppm.

1-(Azidomethyl)-3-bromobenzene (13d): The crude tosylate **14d** (1.31 mmol) in DMF (8 mL) was converted to azide **13d** using NaN_3 (221 mg, 3.40 mmol) according to the above procedure. Purification of the crude product by flash chromatography (petroleum ether/ethyl acetate) gave 148 mg (46%) of azide **13d**. R_f = 0.92 (petroleum ether/ethyl acetate, 1:1). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 54.0 (CH_2), 122.8 (C-3), 126.6 (C-6), 130.4 (C-5), 131.1 (C-2), 131.4 (C-4), 137.6 (C-1) ppm.

1-(Azidomethyl)-4-bromobenzene (13e): The crude tosylate **14e** (1.31 mmol) in DMF (8 mL) was converted to azide **13e** using NaN_3 (221 mg, 3.40 mmol) according to the above procedure. Purification of the crude product by flash chromatography (petroleum ether/ethyl acetate) gave 111 mg (40%) of azide **13e**. R_f = 0.92 (petroleum ether/ethyl acetate, 1:1). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 54.0 (CH_2), 122.3 (C-4), 129.8 (C-5, C-3), 131.9 (C-6, C-2), 134.3 (C-1) ppm.

4-Azido-1-(phenylmethyl)piperidine (13f): The crude tosylate **14f** (1.31 mmol) in DMF (8 mL) was converted to azide **13f** using NaN_3 (221 mg, 3.40 mmol) according to the above procedure. Purification of the crude product by flash chromatography (petroleum ether/ethyl acetate) gave 136 mg (48%) of azide **13f**. R_f = 0.60 (petroleum ether/ethyl acetate, 1:1). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 30.9 (C-3, C-5), 51.2 (C-2, C-6), 57.6 (C-4), 62.9 (CH_2Ph), 127.1, 128.2, 129.0 138.3 (aromatic C) ppm.

3-(2-Azidoethyl)-1*H*-indole (13g): DEAD (133 mg, 0.35 mL of a 40% solution in toluene, 0.77 mmol) was added dropwise to a solution of 2-(1*H*-indol-3-yl)ethanol (82 mg, 0.51 mmol) and Ph_3P (203 mg, 0.77 mmol) in THF (5 mL) at 0 °C. After stirring for 15 min at 0 °C, the nicotinyol azide (98 mg, 0.66 mmol) was added in one portion to the stirred mixture. The reaction mixture was stirred for 12 h during which the mixture reached room temperature. Then all the volatiles were removed in vacuo and the residue subjected to flash chromatography (petroleum ether/ethyl acetate, 1:1), providing the azide **13g** (96 mg, 49%) as a yellow oil.

General Procedure for the 1,3-Dipolar Cu^I-Catalyzed Cycloaddition Reaction: To a solution of the alkyne (1 equiv.) and the azide (1.2 equiv.) in degassed ethanol (0.04 M) was added a degassed solution of $CuSO_4$ (1 M in degassed water, 1.18 equiv.) plus the degassed sodium ascorbate solution (2 M in degassed water, 1.5 equiv.) at room temperature. The reaction mixture was stirred at room temperature for several h (TLC control). Typical reaction times are from 14 to 24 h. After dissapearence of alkyne **1**, the solvent was removed in vacuo and the residue purified by flash chromatography to give the triazoles.

(3*R*)-14-Methoxy-3-{[1-(phenylmethyl)-1*H*-1,2,3-triazol-4-yl]methyl}-3,4,5,6,7,10-hexahydro-1*H*-2-benzoxacyclododecin-1-one (17a): Prepared from alkyne **1** (54 mg, 0.181 mmol) and azide **13a** (29 mg, 0.218 mmol), yield of lactone **17a** 75 mg (96%), colorless amorphous solid. R_f = 0.50 (petroleum ether/ethyl acetate, 1:2). $[\alpha]_D$ = –2.93 (c = 1.0, CH_2Cl_2). ^{1}H NMR (600 MHz, $CDCl_3$): δ = 0.94–1.00 (m, 1 H, 5-H), 1.14–1.21 (m, 1 H, 6-H), 1.33–1.40 (m, 1 H, 6-H), 1.46–1.61 (m, 4 H, 4-H, 5-H, 7-H), 2.06–2.11 (m, 1 H, 7-H), 3.06–3.10 (m, 3 H, 10-H, CH_2-triazole), 3.43 (br. s, 3 H, OCH_3), 3.66 (dd, J = 14.3, 10.4 Hz, 1 H, 10-H), 5.17–5.24 (m, 2 H, 3-H, 9-H), 5.30–5.35 (m, 1 H, 8-H), 5.40 (d, J = 15.1 Hz, 1 H, CH_2Ph), 5.49 (d, J = 15.1 Hz, 1 H, CH_2Ph), 6.67 (d, J = 8.4 Hz, 1 H, 11-H), 6.72 (d, J = 7.4 Hz, 1 H, 13-H), 7.16–7.20 (m, 3 H, aromatic H), 7.24–7.26 (m, 3 H, aromatic H), 7.43 (br. s, 1 H, 5′-H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 19.6 (C-6), 24.5 (C-5), 30.9 (CH$_2$-triazole), 31.8 (C-7), 32.5 (C-4), 37.8 (C-10), 53.9 (CH_2Ph), 55.4 (OCH_3), 71.7 (C-3), 109.7 (C-13), 122.1 (C-5′), 122.7 (C-11), 123.8 (C-14a), 127.8 (C aromatic), 128.5 (C aromatic), 128.7 (C-9), 128.9 (C aromatic), 130.3 (C aromatic), 132.6 (C-8), 134.9 (C aromatic), 139.8 (C-10a), 144.4 (C aromatic), 156.7 (C-14), 167.8 (C-1) ppm. IR (film): $\tilde{\nu}$ = 1272, 1461, 1585, 1716, 2931, 3436 cm^{-1}. MS (EI): m/z (%) = 431 (13), 173 (22), 91 (100), 78 (76). HRMS (ESI): [M + H]$^+$ calcd. for $C_{26}H_{29}N_3O_3$ 432.2282, found 432.2282.

(3*R*)-14-Methoxy-3-{[1-(2-pyridinylmethyl)-1*H*-1,2,3-triazol-4-yl]methyl}-3,4,5,6,7,10-hexahydro-1*H*-2-benzoxacyclododecin-1-one (17b): Prepared from alkyne **1** (54 mg, 0.181 mmol) and azide **13b** (29 mg, 0.218 mmol), yield of lactone **17b** 69 mg (89%), colorless amorphous solid. R_f = 0.45 (petroleum ether/ethyl acetate, 1:2). $[\alpha]_D$ = –3.6 (c = 1.0, CH_2Cl_2). ^{1}H NMR (600 MHz, $CDCl_3$): δ = 0.95–1.02 (m, 1 H, 5-H), 1.15–1.22 (m, 1 H, 6-H), 1.34–1.41 (m, 1 H, 6-H), 1.49–1.61 (m, 3 H, 4-H, 5-H, 7-H), 2.07–2.12 (m, 1 H, 4-H), 3.06–3.11 (m, 3 H, 10-H, CH_2-triazole), 3.61 (br. s, 3 H, OCH_3), 3.66 (dd, J = 14.3, 10.7 Hz, 1 H, 10-H), 5.17–5.26 (m, 2 H, 3-H, 9-H), 5.30–5.35 (m, 1 H, 8-H), 5.61 (d, J = 15.4 Hz, 1 H, CH_2Ph), 5.65 (d, J = 15.4 Hz, 1 H, CH_2Ph), 6.71 (d, J = 8.5 Hz, 1 H, 11-H), 6.72 (d, J = 7.7 Hz, 1 H, 13-H), 7.09 (d, J = 7.7 Hz, 1 H, 3′′-H), 7.16–7.21 (m, 2 H, 12-H, 5′′-H), 7.57 (ddd, J = 7.7, 7.7, 1.5 Hz, 1 H, 4′′-H), 7.65 (br. s, 1 H, 5′-H), 8.49 (d, J = 4.4 Hz, 1 H, 6′′-H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 19.6 (C-6), 24.5 (C-5), 30.8 (CH_2-triazole), 31.9 (C-7), 32.6 (C-4), 37.8 (C-10), 55.4 (CH_2-pyridyl), 55.6 (OCH_3), 71.8 (C-3), 109.7 (C-13), 122.1 (C-3′′), 122.7 (C-11), 122.8 (C-5′), 123.2 (C-5′′), 123.8 (C-14a), 128.7 (C-12), 130.3 (C-4′′), 132.6 (C-9), 137.3 (C-8), 139.8 (C-10a), 144.5 (C-4′), 149.4 (C-6′′), 154.7 (C-14), 156.7 (C-2′′), 167.8 (C-1) ppm. MS (EI): m/z (%) = 432 (18), 340 (42), 187 (22), 174 (47), 145 (84), 93 (100). HRMS (EI): [M + H]$^+$ calcd. for $C_{25}H_{29}N_4O_3$ 433.2234, found 433.2233.

(3*R*)-3-{[1-(1,3-Benzodioxol-5-ylmethyl)-1*H*-1,2,3-triazol-4-yl]-methyl}-14-methoxy-3,4,5,6,7,10-hexahydro-1*H*-2-benzoxacyclododecin-1-one (17c): Prepared from alkyne **1** (30 mg, 0.10 mmol) and azide **13c** (25 mg, 0.14 mmol), yield of lactone **17c** 31 mg (66%), colorless oil. R_f = 0.55 (petroleum ether/ethyl acetate, 2:1). $[\alpha]_D$ = –32.33 (c = 1.3, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.97–1.07 (m, 1 H, 5-H), 1.18–1.28 (m, 1 H, 6-H), 1.37–1.47 (m, 1

H, 6-H), 1.53–1.65 (m, 4 H, 4-H, 5-H, 7-H), 2.11–2.18 (m, 1 H, 7-H), 3.12–3.16 (m, 3 H, 10-H, CH_2-triazole), 3.59 (s, 3 H, OCH_3), 3.71 (dd, J = 14.5, 10.2 Hz, 1 H, 10-H), 5.24–5.29 (m, 2 H, 3-H, 9-H), 5.35–5.40 (m, 1 H, 8-H), 5.34 (d, J = 14.8 Hz, 1 H, CH_2-aryl), 5.43 (d, J = 14.8 Hz, 1 H, CH_2-aryl), 5.92 (d, J = 7.1 Hz, 2 H, OCH_2O), 6.70 (s, 1 H, 4′′-H), 6.73 (s, 2 H, 6′′-H, 7′′-H), 6.76 (d, J = 8.8 Hz, 1 H, 13-H), 6.79 (d, J = 8.1 Hz, 1 H, 11-H), 7.22–7.26 (m, 1 H, 12-H), 7.46 (s, 1 H, 5′-H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 19.7 (C-6), 24.6 (C-5), 31.0 (CH_2-triazole), 31.9 (C-7), 32.6 (C-4), 37.9 (C-10), 53.9 (CH_2-aryl), 55.7 (OCH_3), 71.8 (C-3), 101.3 (OCH_2O), 108.4 (C-13), 108.5 (C-4′′), 109.8 (C-7′′), 121.7 (C-6′′), 121.9 (C-5′), 122.8 (C-11), 123.9 (C-14a), 128.6 (C-5′′), 128.8 (C-9), 130.4 (C-8), 132.7 (C-12), 139.9 (C-10a), 144.5 (C-4′), 147.9 (C-7a′′), 148.3 (C-3a′′), 156.8 (C-14), 167.9 (C-1) ppm. HRMS (EI): $[M + H]^+$ calcd. for $C_{27}H_{30}N_3O_5$ 476.2180, found 476.2177.

(3*R*)-3-({1-[(3-Bromophenyl)methyl]-1*H*-1,2,3-triazol-4-yl}methyl)-14-methoxy-3,4,5,6,7,10-hexahydro-1*H*-2-benzoxacyclododecin-1-one (17d): Prepared from alkyne **14** (30 mg, 0.10 mmol) and azide **13d** (30 mg, 0.14 mmol), yield of lactone **17d** 47 mg (92%), colorless oil. R_f = 0.32 (petroleum ether/ethyl acetate, 1:2). $[\alpha]_D$ = –15.1 (c = 2.4, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.99–1.08 (m, 1 H, 5-H), 1.20–1.31 (m, 1 H, 6-H), 1.37–1.48 (m, 1 H, 6-H), 1.54–1.68 (m, 4 H, 4-H, 5-H, 7-H), 2.12–2.19 (m, 1 H, 7-H), 3.12–3.19 (m, 3 H, 10-H, CH_2-triazole), 3.56 (s, 3 H, OCH_3), 3.73 (dd, J = 14.1, 10.8 Hz, 1 H, 10-H), 5.22–5.33 (m, 2 H, 3-H, 9-H), 5.36–5.42 (m, 1 H, 8-H), 5.43 (d, J = 15.3 Hz, 1 H, CH_2-aryl), 5.53 (d, J = 15.3 Hz, 1 H, CH_2-aryl), 6.77 (d, J = 8.4 Hz, 1 H, 13-H), 6.80 (d, J = 7.6 Hz, 1 H, 11-H), 7.13–7.20 (m, 2 H, 5′′-H, 6′′-H), 7.25 (t, J = 7.9 Hz, 1 H, 12-H), 7.39–7.45 (m, 2 H, 2′′-H, 4′′-H), 7.52 (s, 1 H, 5′-H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 19.7 (C-6), 24.6 (C-5), 31.0 (CH_2-triazole), 31.9 (C-7), 32.5 (C-4), 37.9 (C-10), 53.2 (CH_2-aryl), 55.6 (OCH_3), 71.6 (C-3), 109.8 (C-13), 122.2 (C-5′), 122.8 (C-11), 123.0 (C-3′′) 123.8 (C-14a), 126.4 (C-6′′), 128.7 (C-8), 130.4 (C-12), 130.6 (C-5′′) 130.8 (C-4′′), 131.7 (C-2′′), 132.8 (C-9), 137.2 (C-1′′), 139.9 (C-10a), 144.8 (C-4′), 156.7 (C-14), 167.8 (C-1) ppm. HRMS (EI): $[M + H]^+$ calcd. for $C_{26}H_{29}BrN_3O_3$ 510.1387, found 510.1389.

(3*R*)-3-({1-[(4-Bromophenyl)methyl]-1*H*-1,2,3-triazol-4-yl}methyl)-14-methoxy-3,4,5,6,7,10-hexahydro-1*H*-2-benzoxacyclododecin-1-one (17e): Prepared from alkyne **1** (30 mg, 0.10 mmol) and azide **13e** (30 mg, 0.14 mmol), yield of lactone **17e** 34 mg (67%), colorless oil. R_f = 0,11 (petroleum ether/ethyl acetate, 1:1). $[\alpha]_D$ = –29.3 (c = 1.7, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.97–1.07 (m, 1 H, 5-H), 1.18–1.29 (m, 1 H, 6-H), 1.36–1.47 (m, 1 H, 6-H), 1.52–1.69 (m, 4 H, 4-H, 5-H, 7-H), 2.12–2.19 (m, 1 H, 7-H), 3.10–3.17 (m, 3 H, 10-H, CH_2-triazole), 3.52 (s, 3 H, OCH_3), 3.72 (dd, J = 14.1, 10.6 Hz, 1 H, 10-H), 5.21–5.31 (m, 2 H, 3-H, 9-H), 5.33–5.42 (m, 1 H, 8-H), 5.40 (d, J = 15.3 Hz, 1 H, CH_2-aryl), 5.49 (d, J = 15.3 Hz, 1 H, CH_2-aryl), 6.75 (d, J = 8.4 Hz, 1 H, 13-H), 6.79 (d, J = 7.4 Hz, 1 H, 11-H), 7.08 (d, J = 7.9 Hz, 2 H, 2′′-H, 6′′-H), 7.25 (t, J = 8.1 Hz, 1 H, 12-H), 7.40 (d, J = 8.1 Hz, 2 H, 3′′-H, 5′′-H), 7.47 (s, 1 H, 5′-H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 19.7 (C-6), 24.6 (C-5), 31.1 (CH_2-triazole), 32.0 (C-7), 32.5 (C-4), 37.9 (C-10), 53.3 (CH_2-aryl), 55.6 (OCH_3), 71.7 (C-3), 109.8 (C-13), 122.2 (C-5′), 122.7 (C-4′′), 122.8 (C-11), 123.7 (C-14a), 128.7 (C-8), 129.5 (C-2′′, C-6′′), 130.5 (C-12), 132.1 (C-3′′, C-5′′), 132.8 (C-9), 134.0 (C-1′′), 139.9 (C-10a), 144.8 (C-4′), 156.7 (C-14), 167.8 (C-1) ppm. HRMS (EI): $[M + H]^+$ calcd. for $C_{26}H_{29}BrN_3O_3$ 510.1387, found 510.1390.

(3*R*)-14-Methoxy-3-({1-[1-(phenylmethyl)-4-piperidinyl]-1*H*-1,2,3-triazol-4-yl}methyl)-3,4,5,6,7,10-hexahydro-1*H*-2-benzoxacyclododecin-1-one (17f): Prepared from alkyne **1** (30 mg, 0.10 mmol) and azide **13f** (30 mg, 0.14 mmol), yield of lactone **17f** 32 mg (62%), colorless oil. R_f = 0.15 (petroleum ether/ethyl acetate, 1:1). $[\alpha]_D$ = –28.4 (c = 1.3 in CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.93–1.03 (m, 1 H, 5-H), 1.15–1.26 (m, 1 H, 6-H), 1.31–1.44 (m, 1 H, 6-H), 1.48–1.60 (m, 4 H, 4-H, 5-H, 7-H), 1.94–2.05 (m, 2 H, 3′′-H, 5′′-H), 2.05–2.15 (m, 5 H, 7-H, 2′′-H, 6′′-H, 3′′-H, 5′′-H), 2.93–2.95 (m, 2 H, 2′′-H, 6′′-H), 3.06–3.14 (m, 3 H, 10-H, CH_2-triazole), 3.48 (s, 2 H, CH_2-Ph), 3.66–3.75 (m, 4 H, 10-H, OCH_3), 4.34–4.42 (m, 1 H, 4′′-H), 5.18–5.26 (m, 2 H, 3-H, 9-H), 5.30–5.39 (m, 1 H, 8-H), 6.73–6.76 (m, 2 H, 11-H, 13-H), 7.17–7.28 (m, 6 H, 12-H, aromatic H), 7.49 (s, 1 H, 5′-H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 19.8 (C-6), 24.6 (C-5), 31.0 (CH_2-triazole), 31.9 (C-7), 32.6 (C-4), 32.7 (C-3′′), 32.8 (C-5′′), 37.9 (C-10), 52.0 (C-2′′, C6′′), 56.0 (OCH_3), 58.2 (C-4′′), 62.7 (CH_2-Ph), 71.8 (C-3), 109.9 (C-13), 121.9 (C-5′), 122.8 (C-11), 124.0 (C-14a), 127.2 (C-5′′), 128.3 (C-5′′′, C-3′′′), 128.8 (C-8), 129.0 (C-2′′′, C-6′′′), 130.4 (C-12), 132.7 (C-9), 138.1 (C-1′′′), 139.8 (C-10a), 143.7 (C-4′), 156.9 (C-14), 167.9 (C-1) ppm. HRMS (EI): $[M + H]^+$ calcd. for $C_{31}H_{39}N_4O_3$ 515.3017, found 515.3021.

(3*R*)-3-({1-[2-(1*H*-Indol-3-yl)ethyl]-1*H*-1,2,3-triazol-4-yl}methyl)-14-methoxy-3,4,5,6,7,10-hexahydro-1*H*-2-benzoxacyclododecin-1-one (17g): Prepared from alkyne **1** (30 mg, 0.10 mmol) and azide **13g** (19 mg, 0.12 mmol), yield of lactone **17g** 28 mg (58%), colorless amorphous solid. R_f = 0.48 (petroleum ether/ethyl acetate, 2:1). $[\alpha]_D$ = –22.7 (c = 1.3, CH_2Cl_2). ^{1}H NMR (400 MHz, C_6D_6): δ = 0.87–0.96 (m, 1 H, 5-H), 1.23–1.68 (m, 6 H, 4-H, 5-H, 6-H, 7-H), 1.99–2.06 (m, 1 H, 7-H), 2.94–3.14 (m, 6 H, 10-H, OCH_3, 2′′-H), 3.18 (dd, J = 14.9, 6.1 Hz, 1 H, CH_2-triazole), 3.32 (dd, J = 14.9, 5.8 Hz, 1 H, CH_2-triazole), 4.03 (dd, J = 14.2, 10.4 Hz, 1 H, 10-H), 4.11 (t, J = 6.7 Hz, 1 H, 1′′-H), 5.21–5.33 (m, 1 H, 9-H), 5.38–5.51 (m, 2 H, 3-H, 8-H), 6.32 (s, 1 H, 2′′′-H), 6.33 (d, J = 8.3 Hz, 1 H, 13-H), 6.60 (d, J = 7.3 Hz, 1 H, 11-H), 6.72 (s, 1 H, 5′-H), 6.97 (t, J = 8.0 Hz, 1 H, 12-H), 7.07 (d, J = 7.8 Hz, 1 H, 7′′′-H), 7.12–7.25 (m, 2 H, 5′′′-H, 6′′′-H), 7.34 (s, 1 H, NH), 7.40 (d, J = 7.3 Hz, 1 H, 4′′′-H) ppm. ^{13}C NMR (100 MHz, C_6D_6): δ = 20.0 (C-4), 24.9 (C-3), 26.7 (C-2′′), 31.3 (CH_2-triazole), 32.4 (C-6), 33.2 (C-7), 38.2 (C-10), 50.3 (C-1′′), 55.3 (OCH_3), 72.6 (C-3), 110.0 (C-13), 111.2 (C-3′′′), 111.7 (C-7′′′), 118.5 (C-4′′′), 119.7 (C-5′′′), 122.2 (C-6′′′), 122.6 (C-5′), 122.8 (C-2′′′), 123.1 (C-11), 125.0 (C-14a), 127.3 (C-3a′′′), 129.4 (C-9), 130.3 (C-12), 132.7 (C-8), 136.7 (C-7a′′′), 140.2 (C-10a), 143.6 (C-4′), 157.4 (C-14), 167.9 (C-1) ppm. HRMS (EI): $[M+ Na]^+$ calcd. for $C_{29}H_{32}N_4O_3Na$ 507.2365, found 507.2366.

(3*R*)-14-Hydroxy-3-{[1-(phenylmethyl)-1*H*-1,2,3-triazol-4-yl]-methyl}-3,4,5,6,7,10-hexahydro-1*H*-2-benzoxacyclododecin-1-one (18a): To a stirred solution of the macrolactone **17a** (89 mg, 0.206 mmol) in dry CH_2Cl_2 (4 mL) was added quickly 9-iodo-9-BBN (0.82 mL, 0.82 mmol, 1 M in hexane, 4 equiv.). After 90 s, the reaction was quenched with methanol (12 mL) and the mixture stirred for 1 h. The solvent was removed in vacuo. In order to remove the formed methyl borinate, high vacuum (oil pump) was applied to the flask. This operation (addition of methanol and evaporation of the volatiles) was repeated twice more. Purification of the residue by flash chromatography (petroleum ether/ethyl acetate, 2:1) provided the phenol derivative **18a** (83 mg, 96%) as a colorlessamorphoussolid. R_f=0.53(petroleumether/ethylacetate,2:1). $[\alpha]_D$ = –5.18 (c = 1.0, CH_2Cl_2). ^{1}H NMR (600 MHz, C_6D_6): δ = 0.89–0.99 (m, 1 H, 5-H), 1.12–1.24 (m, 2 H, 4-H, 6-H), 1.28–1.37 (m, 1 H, 6-H), 1.39–1.47 (m, 2 H, 4-H, 5-H), 1.48–1.55 (m, 1 H, 7-H), 2.00–2.06 (m, 1 H, 7-H), 2.50 (dd, J = 14.9, 2.8 Hz, 1 H, CH_2-triazole), 2.65 (dd, J = 14.9, 9.0 Hz, 1 H, CH_2-triazole), 3.09–3.12 (m, 1 H, 10-H), 4.10 (dd, J = 14.0, 10.3 Hz, 1 H, 10-H), 4.78

(br. s, 2 H, CH_2Ph), 5.22–5.31 (m, 2 H, 3-H, 9-H), 5.38–5.43 (m, 1 H, 8-H), 6.46 (s, 1 H, 5′-H), 6.53 (d, J = 7.0 Hz, 1 H, aromatic H), 6.82 (m, 2 H, aromatic H), 6.98–7.02 (m, 4 H, aromatic H), 7.10 (d, J = 7.7 Hz, 1 H, aromatic H), 7.27 (br. s, 3 H, aromatic H, OH) ppm. ^{13}C NMR (150 MHz, C_6D_6): δ = 20.0 (C-6), 25.3 (C-5), 30.5 (CH_2-triazole), 32.7 (C-7), 33.4 (C-4), 38.7 (C-10), 53.8 (CH_2Ph), 70.3 (C-3), 117.8 (C aromatic), 120.8 (C-14a), 121.6 (C-11), 121.7 (C-5′), 128.3 (C aromatic), 128.5 (C-9), 129.0 (C-12), 129.9 (C-8), 131.7 (C aromatic), 132.7 (C aromatic), 135.2 [C aromatic (quaternary)], 140.7 (C-10a), 144.0 (C-4′), 157.5 (C-14), 167.7 (C-1) ppm. MS (EI): m/z (%) = 417 (26), 226 (6), 173 (22), 91 (100). HRMS (ESI): $[M + H]^+$ calcd. for $C_{25}H_{28}N_3O_3$ 418.2125, found 418.2125.

(3*R*)-14-Hydroxy-3-{[1-(2-pyridinylmethyl)-1*H*-1,2,3-triazol-4-yl]methyl}-3,4,5,6,7,10-hexahydro-1*H*-2-benzoxacyclododecin-1-one (18b): To a stirred solution of the macrolactone **17b** (64 mg, 0.148 mmol) in dry CH_2Cl_2 (3 mL) was added quickly 9-iodo-9-BBN (0.59 mL, 0.59 mmol, 1 M in hexane, 4 equiv.). After 90 s, the reaction was quenched with methanol (9 mL) and the mixture stirred for 1 h. The solvent was removed in vacuo. In order to remove the formed methyl borinate, high vacuum (oil pump) was applied to the flask. This operation (addition of methanol and evaporation of the volatiles) was repeated twice more. Purification of the residue by flash chromatography (ethyl acetate) provided the phenol derivative **18b** (42 mg, 67%) as a colorless amorphous solid. R_f = 0.51 (ethyl acetate). $[a]_D$ = –5.05 (c = 2.1, CH_2Cl_2). ^1H NMR (600 MHz, C_6D_6): δ = 0.90–0.98 (m, 1 H, 5-H), 1.11–1.17 (m, 1 H, 6-H), 1.17–1.24 (m, 1 H, 4-H), 1.27–1.34 (m, 1 H, 6-H), 1.39–1.46 (m, 2 H, 4-H, 5-H), 1.48–1.54 (m, 1 H, 7-H), 2.01–2.06 (m, 1 H, 7-H), 2.53 (dd, J = 14.9, 2.8 Hz, 1 H, CH_2-triazole), 2.66 (dd, J = 14.9, 9.0 Hz, 1 H, CH_2-triazole), 3.10 (ddd, J = 14.0, 5.2, 2.6 Hz, 1 H, 10-H), 4.10 (dd, J = 14.0, 10.3 Hz, 1 H, 10-H), 5.04 (d, J = 15.4 Hz, 1 H, CH_2-pyridyl), 5.08 (d, J = 15.4 Hz, 1 H, CH_2-pyridyl), 5.20–5.30 (m, 2 H, 3-H, 9-H), 5.38–5.43 (m, 1 H, 8-H), 6.51–6.54 (m, 2 H, 5′′-H, 11-H), 6.66 (d, J = 7.7 Hz, 1 H, 3′′-H), 6.84 (s, 1 H, 5′-H), 6.92 (ddd, J = 7.7, 7.7, 1.8 Hz, 1 H, 4′′-H), 7.00 (dd, J = 8.1, 7.4 Hz, 1 H, 12-H), 7.08 (dd, J = 8.1, 0.7 Hz, 1 H, 13-H), 8.27 (d, J = 4.4 Hz, 1 H, 6′′-H) ppm. ^{13}C NMR (100 MHz, C_6D_6): δ = 19.9 (C-6), 25.2 (C-5), 30.4 (CH_2-triazole), 32.7 (C-7), 33.3 (C-4), 38.7 (C-10), 55.4 (CH_2-pyridyl), 70.3 (C-3), 117.7 (C-13), 121.1 (C-14a), 121.5 (C-5′′), 122.3 (C-3′′), 122.7 (C-5′), 123.0 (C-11), 129.8 (C-9), 131.6 (C-12), 132.8 (C-8), 137.0 (C-4′′), 140.6 (C-10a), 143.9 (C-4′), 149.5 (C-6′′), 155.0 (C-14), 157.3 (C-2′′), 167.7 (C-1) ppm. MS (EI): m/z (%) = 418 (30), 174 (16), 145 (83), 109 (31), 93 (100). HRMS (ESI): $[M + H]^+$ calcd. for $C_{24}H_{27}N_4O_3$ 419.2078, found 419.2077.

Supporting Information Available: (see also the footnote on the first page of this article): Copies of ^1H and ^{13}C NMR spectra of the alcohols **7**, **8**, and all triazoles.

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