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Two Versatile and Parallel Approaches to Highly Symmetrical Open and Closed Natural Product-Based Structures

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Dedicated to Professor Antonio García-Martínez (UCM) on the occasion of his retirement

Abstract: Two parallel approaches for preparing diverse and highly symmetrical homohybrids derived from a series of mono- and diterpenes, steroids, and alkaloids are reported. Both procedures are based on the mono-addition of bis(alkynyl) dilithium reagents to natural products having a carbonyl group to produce the corresponding alkynyl derivatives. The Glaser–Hay Cu-promoted homocoupling of these alkynyl natural product mono-adducts as well as the Huisgen Cu-catalyzed azide–alkyne cycloaddition (CuAAC) reaction resulted in the synthesis of steroid-, terpene-, and alkaloid-based homohybrid derivatives incorporating diverse spacers to join the natural product scaffolds. Straightforward entries to novel closed highly symmetrical and complex estrone-based macrocyclic and cage architectures by means of the Glaser–Eglinton homocoupling and the CuAAC reaction have been devised.

Keywords: alkyne homocoupling · click chemistry · diversity-oriented synthesis (DOS) · molecular cages · natural products

Introduction

Although in the last decades there has been growing interest in the development of methods for preparing large libraries of new compounds, it has recently been recognized that the number of compounds does not determine the quality of a library; rather, among other factors, the quality is determined by the diversity.[1] In this context, one of the current tendencies is the preparation of small focused collections of synthetic natural product hybrids,[2] made as combinations of fragments from different natural products within the diversity-oriented synthesis (DOS) concept.[3] The main advantage of this strategy is the preparation of an unlimited number of highly diverse molecular entities without relying on the isolation of natural products from their natural sources. In order to implement this approach, general and efficient methodologies are required. Thus, procedures based on metathesis (cross-metathesis, CM[4a–c] and ring-closing metathesis, RCM[4d–f]) and on the Huisgen Cu-catalyzed azide–alkyne cycloaddition (CuAAC) "click" reaction have been used to prepare natural product hybrids.[5] In our ongoing research devoted to the development of methodologies for preparing natural product hybrids by using transition metal catalysts and reagents, we have recently shown that natural product-based homodimers and homotrimers can be built by creating the tether joining the monomeric subunits by metathesis, as in the case of compound **1**,[6] through the Co-promoted cyclodimerization and cyclotrimerization of appropriately functionalized natural product monomers, as in the case of dimer **2**,[7] and by means of the Nicholas approach, as exemplified by product **3**[8] (Figure 1).

In parallel, we have also reported methodologies for the synthesis of complex natural product-based macrocycles through the Nicholas approach[9] and by sequential CuAAC–Glaser–Eglinton homocoupling.[10] The preparations of highly symmetrical natural product-based macrocycles such as **4** and **5** exemplify the versatility of these ap-

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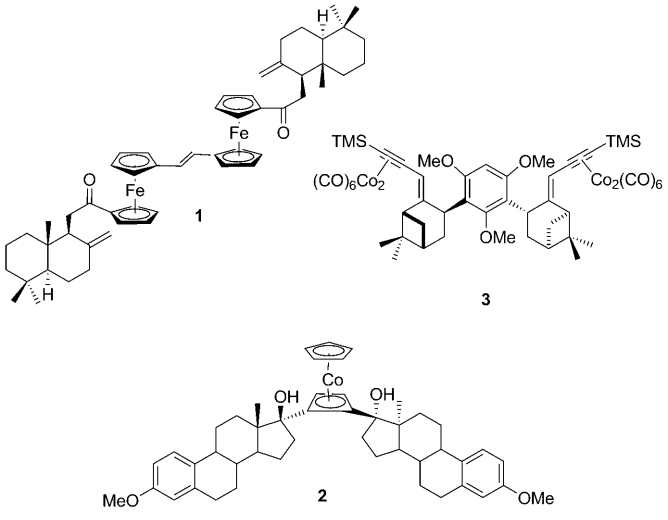
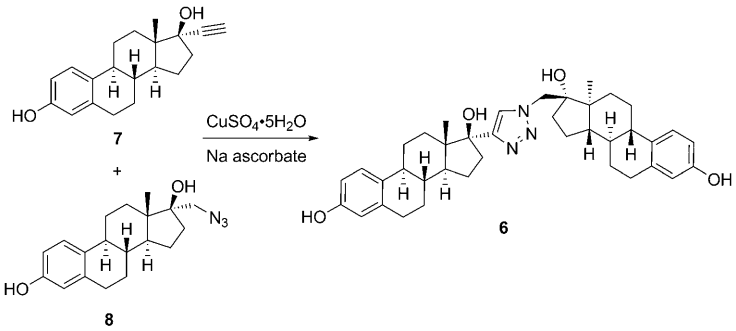


Figure 1. Natural product-based homodimers.

proaches (Figure 2). Therefore, our work has shown how the attachment of an alkynyl group to a natural product provides a key appendage for generating new structures, in which the diversity may be variously introduced in the natural product scaffold, in the structure of the alkyne, or in a reaction to which the terminal alkyne is later submitted.[7–10]

With these premises in hand, we devised two approaches to access symmetrical open, macrocyclic, and eventually cage structures based on natural products, by switching the reactivity of the terminal alkynyl groups by means of either Cu-promoted homocoupling or the Huisgen Cu-catalyzed azide–alkyne cycloaddition (CuAAC) processes. In addition, these methodologies conform to the diversity-oriented synthesis concept (DOS).[3] It is remarkable to note that in spite of the increasing number of applications of Cu-promoted acetylenic coupling[11] and of the click[12] methodology in organic synthesis, they have been scarcely employed to prepare natural product homohybrids.

Thus, the Cu-promoted homocoupling of terminal alkynes has been used to prepare only a few naturally occurring di- and polyacetylenes,[11d] despite the fact that the first steroid-based dimers[13] were synthesized nearly 50 years ago. On the other hand, the CuAAC reaction has been profusely employed for the modification of primary metabolites.[14,15] However, the use of this click methodology for the synthesis of natural product hybrids remains little studied.[5] The synthesis of dimer **6**[16] by reaction of ethynylestradiol (**7**) with azide **8**, together with the preparation of bile acid dimers and oligomers,[17] are two of the rare examples of the preparation of natural product homohybrids by using a click approach (Scheme 1).



Scheme 1. Steroid dimer **6** derived from ethynylestradiol (**7**).

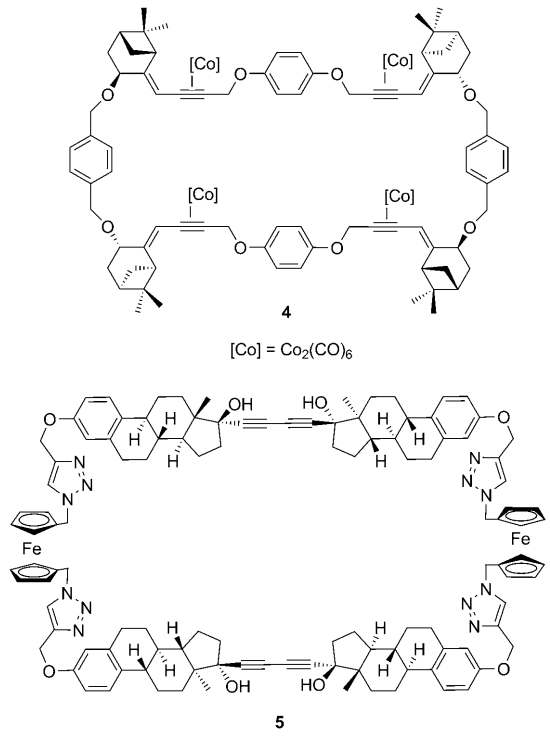


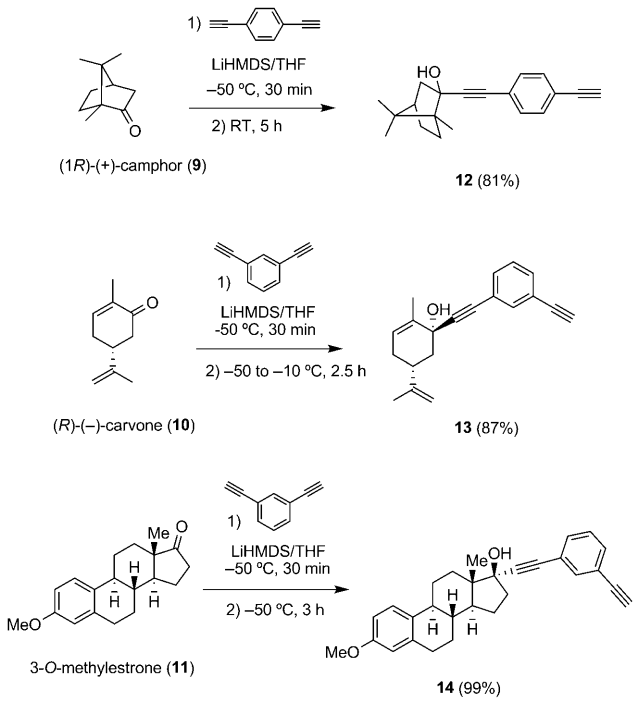
Figure 2. Tetrameric natural product-based macrocycles obtained by the Nicholas approach and through sequential CuAAC–Glaser–Eglinton homocoupling.

We report herein the mono-addition of bis(alkynyl) dilithium reagents to various natural products bearing a carbonyl group to produce the scaffolds needed for accessing diverse natural product hybrids, either by Cu-promoted oxidative homocoupling or by Huisgen Cu-catalyzed azide–alkyne cycloaddition (CuAAC). In this way, highly symmetrical homohybrids having novel complex open and closed estrone-based architectures could be accessed. These selective, efficient, and versatile procedures should prove useful for obtaining remarkable diverse and complex structures having defined geometries.

Results and Discussion

Preparation of alkynyl natural product-derived scaffolds: The preparation of alkynyl natural product derivatives was first pursued by using robust natural products such as the monoterpenes (1*R*)-(+)-camphor (**9**) and (*R*)-(−)-carvone (**10**), as well as the steroid 3-*O*-methylestrone (**11**) (Scheme 2). After tuning the reaction conditions **9**, **10**, and

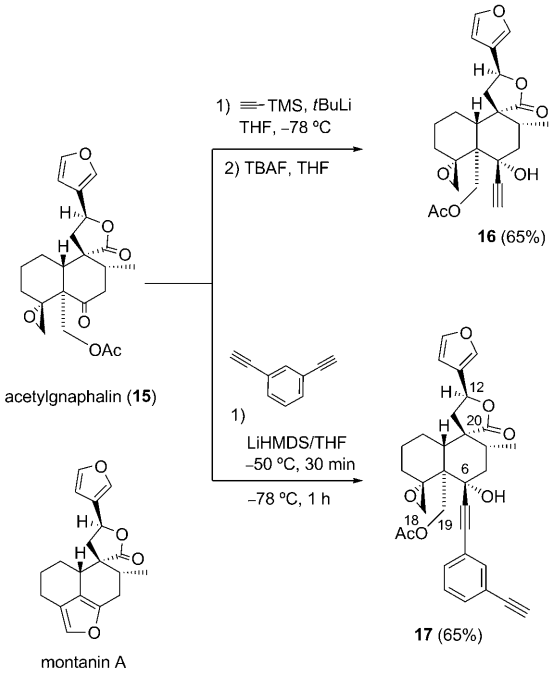
11 were each reacted with an excess of the aromatic bis-(alkynyl) dilithium reagent derived from 1,3- or 1,4-diethynylbenzene to selectively afford the corresponding mono-adducts **12**,[18] **13**,[19] and **14**[20] as the sole reaction products in isolated yields of 81–99%.



Scheme 2. Preparation of the alkynyl natural product derivatives **12**–**14**.

The compatibility of this protocol with highly functionalized and sensitive natural products was then investigated. In this context, we chose the diterpene 19-acetylgnaphalin (**15**),[21] since it bears an impressive array of functionalities and is extremely prone to rearrangement to montanin A.[22] Prior to the use of a bis(alkynyl) lithium reagent, we reacted 19-acetylgnaphalin (**15**) with one equivalent of TMS-acetylide in THF at −78 °C. Treatment of the reaction product with tetrabutylammonium fluoride (TBAF) produced the alkynyl derivative **16** in 65% isolated yield (two steps) (Scheme 3). Analogously, reaction of 19-acetylgnaphalin (**15**) with the lithium reagent prepared "in situ" by deprotonation of 1,3-diethynylbenzene with lithium hexamethyldisilazanide (LiHMDS) in THF at −78 °C produced **17** as the sole reaction product in 65% yield (Scheme 3).[23] Analytical and spectroscopic data for the reaction products **16** and **17** were in agreement with the proposed structures,[24] establishing that the addition of the organolithium reagent at the C-6 position of the diterpene framework took place at the β face of the decalin system.[25] Therefore, the addition of the organolithium reagents derived from TMS-acetylene and 1,3-diethynylbenzene allows the efficient introduction of the required alkyne terminus in 19-acetylgnaphalin (**15**).

Finally, the terminal alkynyl moiety was appended to the alkaloid reserpine (**18**) by reaction with propargyl bromide



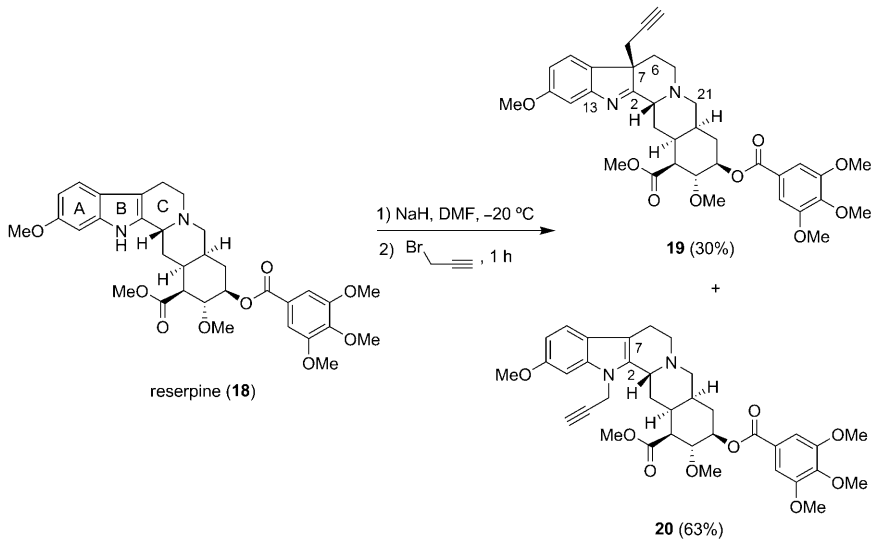
Scheme 3. Preparation of terminal alkynyl derivatives from 19-acetylgnaphalin (**15**).

in the presence of NaH in DMF. Regioisomers **19** and **20** were obtained in isolated yields of 30 and 63%, respectively (Scheme 4).

The structures of reaction products **19** and **20** were established by comparison of their NMR spectra with those of related derivatives; complete assignments of their ^{1}H and ^{13}C NMR spectra were made on the basis of 2D NMR experiments (*g*HSQC and *g*HMBC).[26] In the case of the *C*-alkylated derivative **19**, the stereochemistry at the newly formed quaternary center C-7 was determined on the basis of NOE experiments. Irradiation of proton H-3β at $\delta =$ 4.05 ppm produced an enhancement of the intensity of the signals attributable to H-21β ($\delta = 3.28$ ppm) and the propargylic methylene protons at $\delta = 2.84$ and 2.23 ppm. Enhancement of the overlapped signals at $\delta = 2.10$ ppm was also observed. This fact places proton H-3β and the propargylic CH_2 carbon on the same side of the molecule.

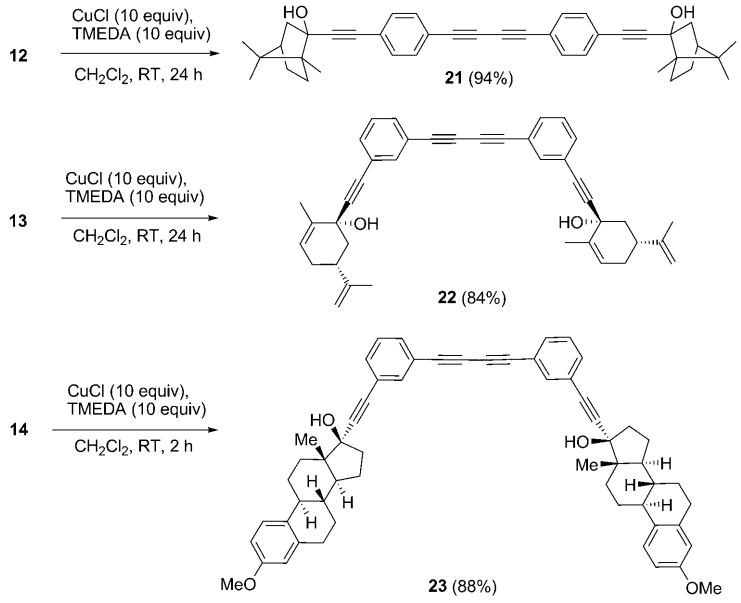
Having developed the synthetic methodology for obtaining the natural product derivatives bearing the required alkyne termini, we undertook the synthesis of natural product oligomeric homohybrids, macrocycles, and molecular cages by making use of the alkyne reactivity.

We first examined the synthesis of dimeric homohybrids through the Cu-mediated oxidative homocoupling of the natural product-derived terminal alkynes **12**–**14**. Thus, reactions of **12**–**14** with CuCl/TMEDA (TMEDA = *N*,*N*,*N*′,*N*′-tetramethylethylenediamine) yielded the corresponding dimers **21**, **22**, and **23** in isolated yields of 94%, 84%, and 88%, respectively (Scheme 5). The structures of the reaction products **21**–**23** were established on spectroscopic grounds. In all cases, the ^{1}H and ^{13}C NMR spectra were devoid of the



Scheme 4. Preparation of terminal alkynyl derivatives from reserpine (**18**).

characteristic pattern of signals due to a terminal alkyne fragment.[27] Instead, signals attributable to a symmetrically substituted 1,3-butadiyne framework appeared. In addition, the mass spectra of **21** (ESI), **22** (APCI), and **23** (ESI) showed peaks at *m*/*z* 537.5 $[M-H_2O+H]^+$, 533 $[M+H-H_2O]^+$, and 783 $[M+H-2H_2O]^+$, respectively, confirming that these products were indeed dimers of the corresponding starting alkynes **12**–**14**.

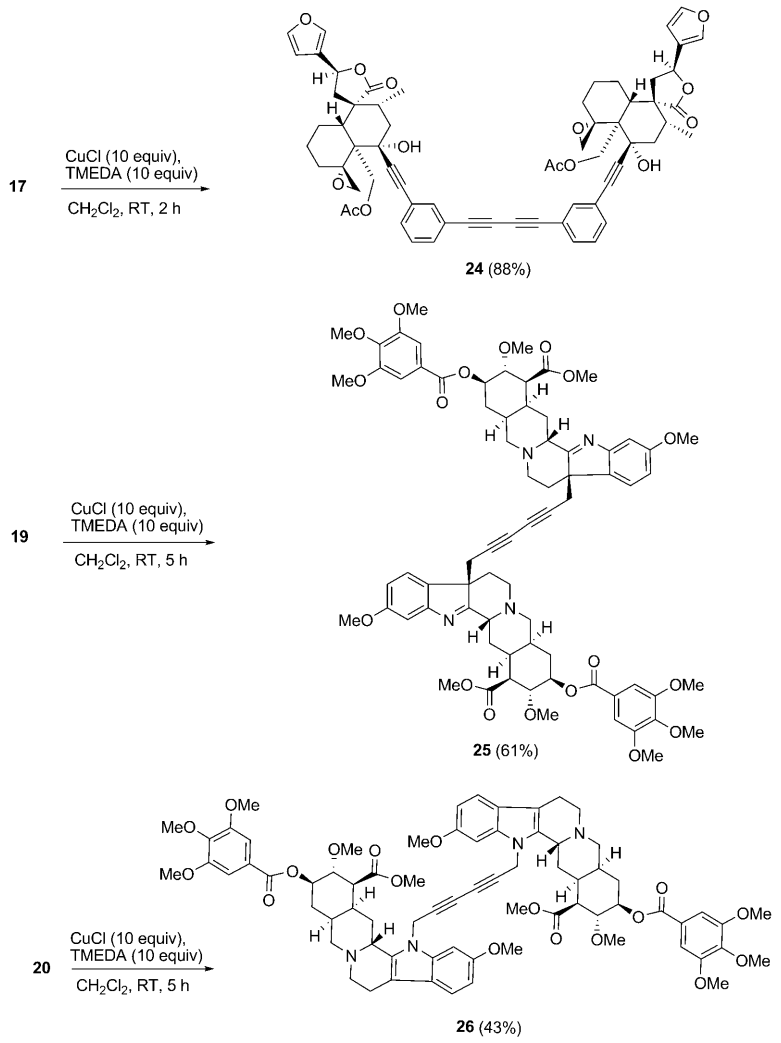


Scheme 5. C_2-symmetric bis(alkynyl)-tethered homohybrids derived from (1*R*)-(+)-camphor (**9**), (*R*)-(−)-carvone (**10**), and 3-*O*-methylestrone (**11**).

We proceeded to investigate the compatibility of these reaction conditions with more functionalized scaffolds. Thus, the 19-acetylgnaphalin derivative **17** was treated with CuCl/TMEDA under the standard conditions to afford dimer **24** in 88% isolated yield (Scheme 6). In the same manner, the *C*- and *N*-alkylated reserpine derivatives **19** and **20** produced dimers **25** and **26** in isolated yields of 61 and 43%, respectively. The ^1H and ^{13}C NMR data for homohybrids **24**–**26** were in agreement with the proposed structures,[28] as were the mass spectra, which showed peaks at *m*/*z* 1077.3 $[M+Na]^+$ for **24** (ESI) and 1291 $[M+H]^+$ for **25** and **26** (APCI), establishing that they were dimers of the starting alkynes **17**, **19**, and **20**, respectively. From a structural point of view, it has to be mentioned that all of the dimeric compounds synthesized in the course of this work have one binary symmetry axis, so that their ^1H and ^{13}C NMR spectra account for half of the molecule, thus featuring a single set of signals for the two natural product fragments. These results demonstrate the usefulness of our two-step protocol for preparing functionalized polyalkynyl-tethered homodimeric natural product derivatives. This methodology allows the preparation of C_2-symmetric dimers having either a rigid bis(diethynyl)benzene motif (compounds **21**–**24**, Schemes 5 and 6) or a shorter 1,3-butadiyne bridge (compounds **25** and **26**, Scheme 6).

Next, the CuAAC reaction was tested as a parallel approach to natural product-based homodimers. This protocol allows the introduction of different tethers by varying the nature of the azide, thereby providing a point for introducing structural diversity. The Cu-catalyzed cycloaddition reaction was first tested with the commercially available and robust steroid mestranol (**27**). Reactions of one equivalent of azides **28a**–**c** with two equivalents of **27**, in the presence of catalytic amounts of $CuSO_4 \cdot 5H_2O$ (10–30 mol%) and sodium L-ascorbate (20–60 mol%) in DMF at RT, gave compounds **29a**–**c** in excellent yields (Scheme 7). Treatment of mestranol (**27**) with the ferrocene-bis(azide) **28b** required a higher loading of $CuSO_4 \cdot 5H_2O$ (30 mol%) and a longer reaction time (6.5 h) to form the corresponding bis(steroid) **29b** in 90% isolated yield.

Next, we turned our attention to the more functionalized reserpine derivative **20**. Reaction of alkyne **20** with diazides **28a**,**b**, in the presence of catalytic amounts of $CuSO_4 \cdot 5H_2O$ (10–30 mol%) and sodium L-ascorbate (20–60 mol%) in DMF at RT, yielded dimeric alkaloids **30a** and **30b**[29] in good isolated yields (Scheme 8). Analogously, submitting the *C*-propargyl reserpine derivative **19** to the same reaction conditions with azide **28a** led to the alkaloid-based dimer **31**. In all cases, the structural and stereochemical integrity of the reserpine nucleus was maintained (Scheme 8).



Scheme 6. C_2-symmetric bis(alkynyl)-tethered homohybrids derived from 19-acetylgnaphalin (**15**) and reserpine (**18**).

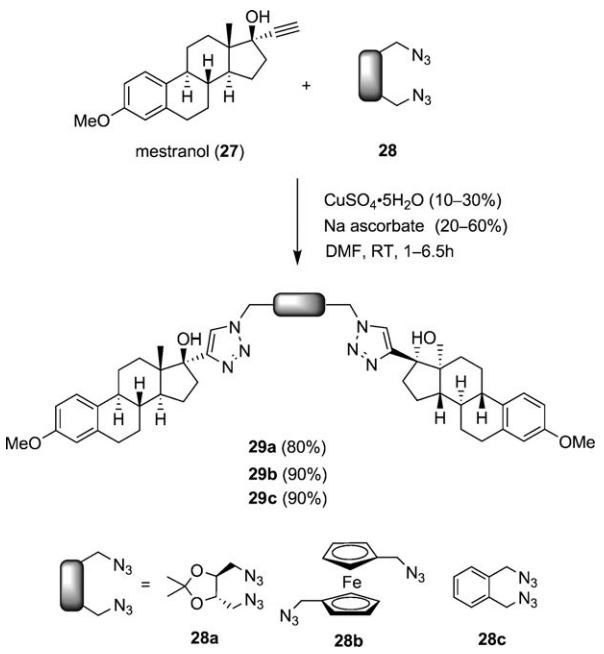
The structures of compounds **29a–c**, **30a**,**b**, and **31** were established by spectroscopic means. The ^{1}H and ^{13}C NMR data for each of the dimers showed a single set of signals for the two natural product fragments, as expected for molecules having a C_2 symmetry axis.[30] Likewise, the ESI mass spectra of the coupled compounds **29a–c** showed peaks at *m*/*z* 797.5 $[M+H-H_2O]^+$, 917 $[M+H]^+$, and 773.3 $[M+H-H_2O]^+$, respectively. Dimers **30a** and **31** derived from reserpine showed peaks at *m*/*z* 1505.6 $[M+H]^+$ and 1506.2 $[M+H]^+$, while compound **30b** gave rise to a signal at *m*/*z* 1589 $[M+H]^+$. All of the above data are consistent with the attachment of two natural product fragments to the corresponding diazides **28a–c**, in full accordance with the proposed structures.

Clearly, the CuAAC protocol is an effective method for preparing dimeric steroids and *N*- and *C*-linked dimeric alkaloids. To study the usefulness of this approach for preparing sensitive functionalized natural product-based dimers, alkynyl derivatives **16** and **17** were reacted with bis(azide) **28a** (Scheme 9). Under the standard conditions, the corresponding dimers **32a** and **33** were obtained in isolated yields of 86 and 90% after 5 h and 1.5 h of reaction, respectively. Furthermore, cycloaddition of compound **16** and ferrocenyl azide **28b** yielded the bioorganometallic dimer **32b** in 22% yield (89% based on recovered starting material). A higher catalyst loading (30 mol%) and a longer reaction time (23 h) were required in this case (Scheme 9). It should be noted that 76% of the 19-acetylgnaphalin derivative **16** was recovered unaltered.[31] The spectroscopic data for coupled compounds **32a**,**b** and **33** are in full agreement with their proposed structures.[32]

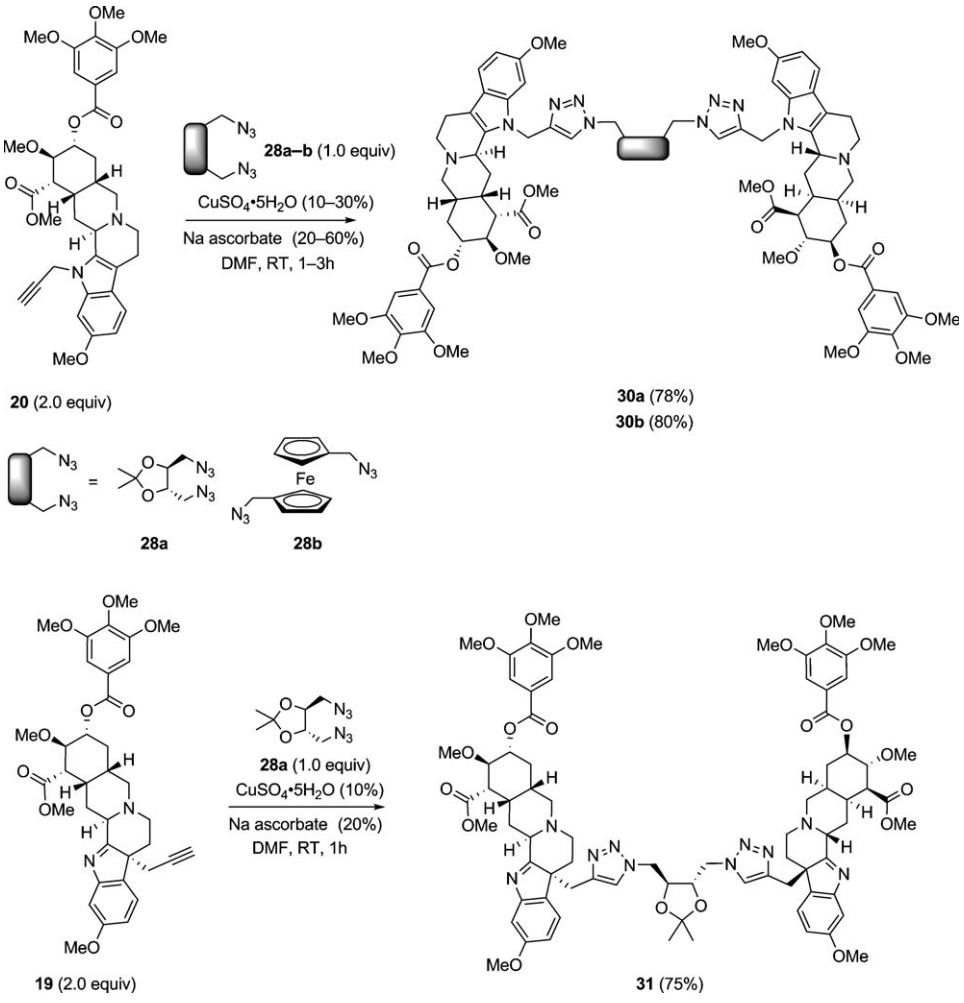
The obtained results prove the compatibility of the Glaser–Hay Cu-promoted oxidative homocoupling and CuAAC click reactions with a range of natural products, from robust steroids to sensitive, highly functionalized diterpenes and alkaloids. It is worth emphasizing that diverse natural product homodimers can be prepared à la carte from a single alkyne by choosing the coupling protocol. Moreover, structural diversity can be introduced by appropriate choice of the coupling reaction, the length of the tether (by selecting the azide, the alkyne moiety, or both), and the nature of the natural product scaffold. The fact that there is a clear relationship between the structures of some dimeric natural products and the induction of dimerization in proteins may make this approach especially attractive.[33]

In addition to C_2-symmetric dimers, the CuAAC reaction provides a general entry to trimeric and tetrameric structures owing to the possibility of using tri- and tetra-azides. Thus, mestranol (**27**) was independently reacted with triazide **34a** and tetraazide **35** under standard click conditions to afford the corresponding trimeric and tetrameric homohybrids **36** and **37** in excellent isolated yields (Scheme 10).

The structures of compounds **36** and **37** were established by spectroscopic means. Electrospray MS analysis of **36** showed two signals at *m*/*z* 1196.6 and 1120.3 attributable to the ions $[M+Na]^+$ and $[M+H-3H_2O]^+$, respectively, consistent with the attachment of three fragments derived from mestranol (**27**) to spacer **34a**. Likewise, tetramer **37** dis-



Scheme 7. C_2-symmetric homohybrids derived from mestranol (**27**).



Scheme 8. C_2-symmetric homohybrids derived from reserpine (**18**).

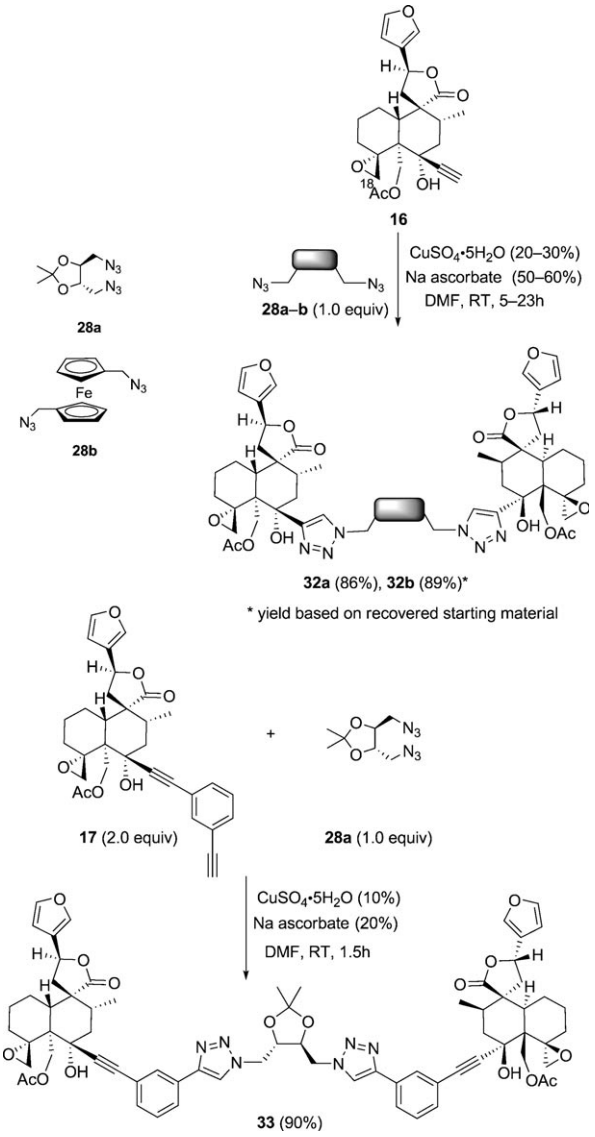
played a signal at m/z 1562.8 corresponding to the ion $[M+Na]^+$. The ^1H and ^{13}C NMR data for **36** and **37** account for one-third and one-quarter of the molecules, as expected for compounds having one C_3-symmetry axis and three C_2-symmetry axes, respectively (Scheme 10).[34]

Synthesis of closed oligomers—macrocycles and cages: Having demonstrated that diverse dimeric and oligomeric natural product-based structures can be easily obtained from either commercial or readily available alkynyl derivatives of natural products, we proceeded to investigate the building of macrocyclic and cage-like steroid-derived architectures using either the Cu-mediated oxidative homocoupling or the CuAAC protocol.[35]

In our previous work,[10] it was established that the combination of rigid steroid scaffolds **38** with pre-organized triazole spacers produces semicavities **39** (Scheme 11). Compounds **39** form macrocycles in good yields by dimerization using the Glaser protocol, in spite of this reaction being kinetically controlled.[36] Evidently, effecting a second CuAAC reaction on bis(alkynyl) dimers **39** by using a series of capping diazides **28** will yield the desired C_2-symmetric dimeric macrocycles **40**. Scaffold-based diversity may be sequentially introduced in both click reactions by combining different diazides. Thus, semicavities **39a**, **39b**, and **39c** were successfully ring-closed to form macrocycles **40ab** (42%), **40bc** (44%), **40cc** (57%), and **40cd** (38%) by reaction with azides **28b**, **28c**, and **28d** as appropriate (Scheme 11).

The structures of the chiral cavities **40** were established on spectroscopic grounds. Their ^1H and ^{13}C NMR data showed a single set of signals for both steroid fragments, as expected for an architecture possessing a C_2 symmetry axis. In addition, ESI mass spectra of macrocycles **40ab**, **40bc**, **40cc**, and **40cd** showed signals at m/z 1178, 1153, 1046, and 1047, corresponding to the respective $[M+H]^+$ ions, thus confirming the proposed structures.

Access to more rigid macrocycles having four estrone fragments joined by four units of 1,3-butadiyne was devised by using the Cu-promoted oxidative coupling. This approach requires the accomplishment of two sequential Cu-promoted



Scheme 9. C_2-symmetric homohybrids derived from 19-acetylgnaphalin (**15**).

homocoupling reactions on a bis(alkynyl)estrone derivative. Bis(alkyne) **38**, the starting material for the click macrocycles **40**, has two differentiated alkyne termini and thus represents a suitable derivative for executing this strategy.

Thus, a sequential synthesis of the estrone-based macrocycle **41** was accomplished (Scheme 12). Submission of **38** to the Hay conditions for 16 h yielded the corresponding dimer **42** in 89% yield. Removal of the TMS groups by treatment with TBAF afforded the semicavity **43** required to perform the crucial macrocyclization step. The homocoupling of **43** under the Eglinton conditions ($Cu(OAc)_2 \cdot H_2O/CH_3CN$-Py)[37] nicely formed the expected tetrameric macrocycle **41** in a respectable 66% yield (Scheme 12), together with the C_4-symmetric oligomer **44** (Figure 3).[38] The macrocyclic structures of compounds **41** and **44** were unequivocally confirmed by their ESI mass spectra, which showed peaks at m/z 1294.8 $[M-2H_2O+H]^+$ and m/z 2682.5 $[M+Na]^+$, respectively. These results proved the proposed structures and indicated the presence of eight steroid fragments in macrocycle **44**. In addition, the ^1H and ^{13}C NMR data for macrocycles **41** and **44** showed a single set of signals for the estrone fragments, as expected for these highly symmetrical architectures possessing three C_2-symmetry axes and one C_4-symmetry axis, respectively. Efforts to modulate the size and the functionality of the macrocycles are in progress in our laboratories.

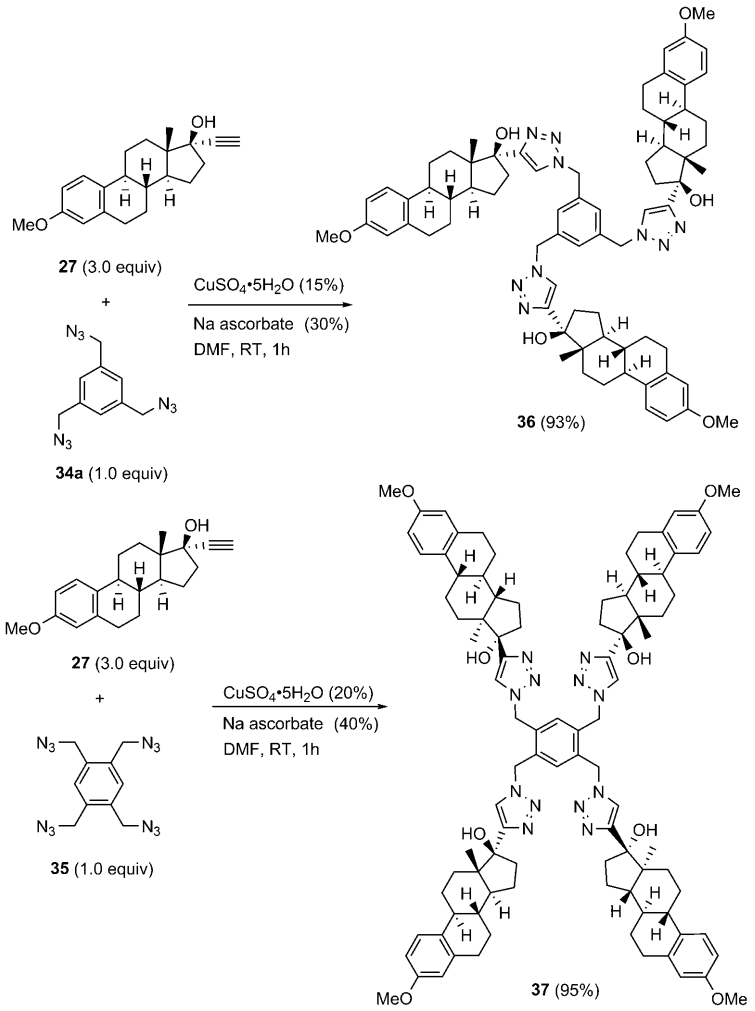
Finally, using both the acetylenic homocoupling and the CuAAC protocols, the synthesis of natural product-based C_3-symmetric cages was pursued. The vast majority of the reported cage-like architectures prepared through the acetylenic coupling have been based on rigid conjugated diynyl and polyynyl aromatic chains or combinations thereof, and have had little or no functionalization.[11d] As far as we are aware, there have been no reports concerning the use of natural products as building blocks in the construction of such architectures through these approaches.[39]

The scaffold to build a C_3-symmetric cage required the incorporation of three identical terminal alkynyl moieties to carry out either three simultaneous homocouplings or Cu-mediated cycloadditions in the final decisive step. First, the attachment of three alkynylestrone fragments to different cores using the CuAAC protocol was pursued (Scheme 13). Thus, monoprotected bis(alkynyl) building block **38**[10] was reacted with triazides **34a–c** to afford trimers **45a** (71%), **45b** (75%), and **45c** (72%), treatment of which with TBAF produced tripods **46a** (98%), **46b** (91%), and **46c** (88%).

Attempts to cap trimers **46a** and **46c** with triazides **34a** or **34c** under standard CuAAC conditions proved unsuccessful, producing large amounts of polymeric materials. The failure to generate molecular cages from trimers **46a** and **46c** could be due to their lack of pre-organization. In contrast, tripod **46b**, derived from bis(alkynyl) building block **38** and 1,3,5-tris(azidomethyl)-2,4,6-triethylbenzene (**34b**), produced the desired molecular cage **47** in 25% isolated yield when submitted to the CuAAC protocol with triazide **34c** (Scheme 13). Evidently, the pre-organization imposed by the 1,3,5-triethylbenzene[40] core of azide **34b** allows tripod **46b** to react with azide **34c** in a productive way, resulting in closure of the cage. The structure of cage **47** was confirmed by its ESI mass spectrum, which featured a peak at m/z 1527.3 corresponding to the $[M+H]^+$ ion.

It is remarkable that, in contrast to the highly symmetrical oligomeric homohybrids prepared throughout this work, the ^1H and ^{13}C NMR data for **47** did not show a single set of signals for the three steroid units (see the Experimental Section). Nevertheless, its ^{13}C NMR spectrum was devoid of signals attributable to any of the terminal alkyne moieties of the precursor **46b**.[41] It should be noted that a flexible triazide like **34c** is required for the capping of tripods **46** to yield the corresponding cages. Thus, attempted reactions of **46** with azides **34a**,**b** were unsuccessful.

Finally, we developed an entry to steroid-based C_3-symmetric cages by performing three simultaneous Cu-promot-



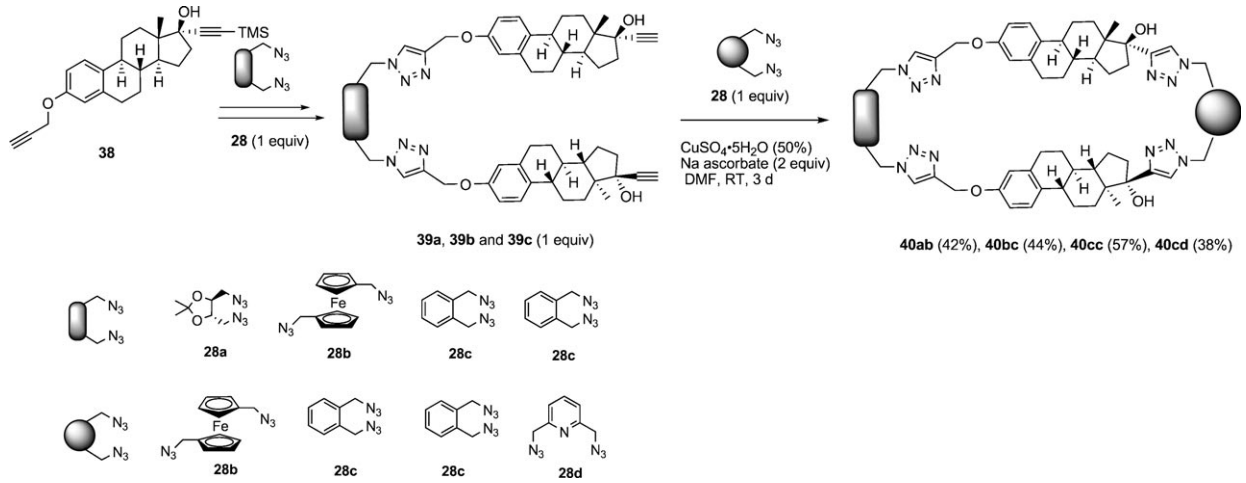
Scheme 10. Trimer **36** and tetramer **37** derived from mestranol (**27**).

ed oxidative homocouplings on trialkynyl-based estrone scaffolds (Scheme 14).

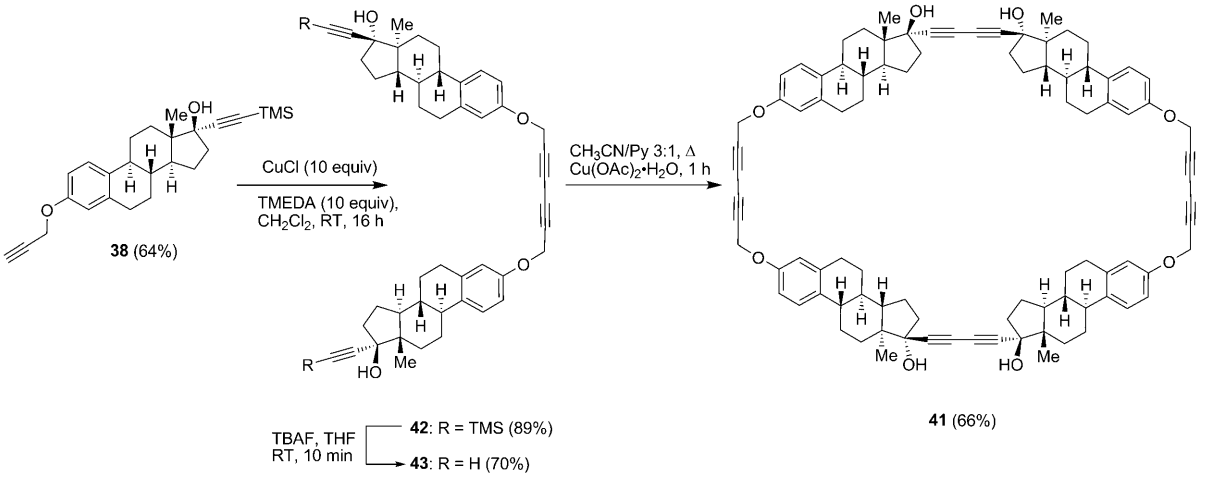
In the light of the discussed results, the C_3-symmetric tripod **48** bearing three estrone units was prepared by alkylation of three equivalents of estrone (**49**) with one equivalent of 1,3,5-tris(bromomethyl)-2,4,6-triethylbenzene[42] in the presence of NaH in DMF at 70 °C (Scheme 14). Terminal alkyne groups were then incorporated at the carbonyl groups of estrone-based trimer **48** by treatment with lithium TMS-acetylide, yielding **50**. Removal of the TMS groups yielded tripod **51** bearing three terminal alkynyl groups. Compound **51** was ultimately submitted to the Eglinton conditions, yielding the desired C_3-symmetric hexameric estrone-based cage **52** in a remarkable 41 % yield. Other standard Cu–acetylene coupling-based methodologies were tested, but without any substantial improvement in yield.[43]

Cage **52** possesses one C_2- and one C_3-symmetry axis, and its ^{1}H and ^{13}C NMR spectra showed a single set of signals for the six steroid fragments. The structure of **52** was unequivocally confirmed by its MALDI mass spectrum, which showed two peaks at m/z 2191.3 $[M+Na]^+$ and 2207.3 $[M+K]^+$. As far as we are aware, this is the first example of a natural product-based cage prepared by acetylenic coupling.[39]

It is worth noting that while most efforts have been focused on the preparation of supramolecular cages, the effi-



Scheme 11. C_2-symmetric macrocycles prepared from estrone-derived bis(alkyne) **38**.



Scheme 12. Tetrameric macrocycle **41** from estrone-derived bis(alkyne) **38**.

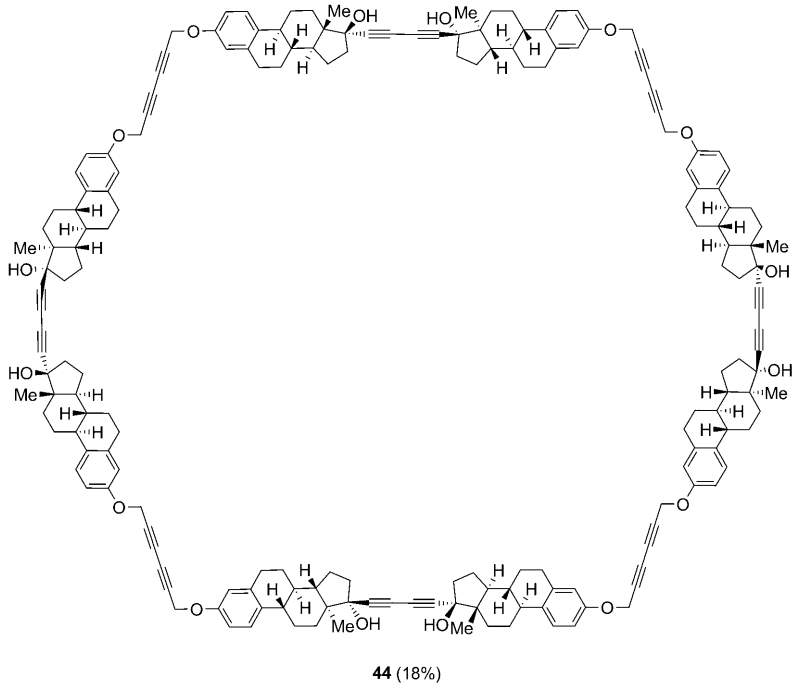
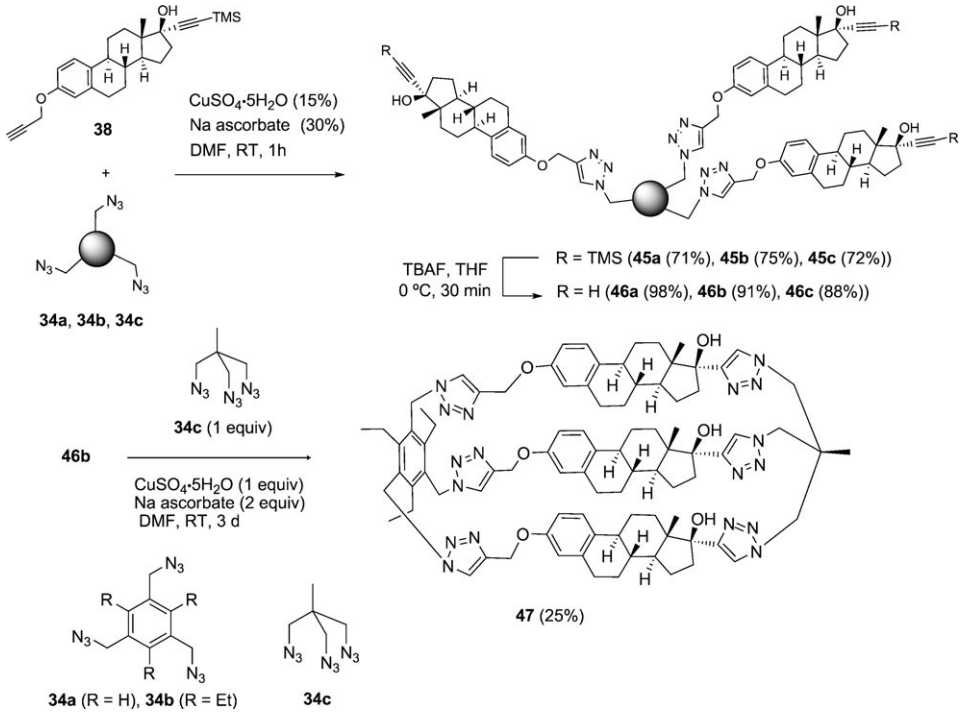


Figure 3. C_4-symmetric macrocycle prepared from bis(alkyne) **38**.

cient covalent assembly of cage-like structures still remains a challenge. In this context, the above described approach to estrone-based cages **47** and **52** could be useful for application to other natural products and represents an entry to molecular architectures having very different structural designs. The study of these chiral cavities as host molecules is underway in our laboratories.

Conclusion

Two parallel approaches for preparing diverse and complex C_2- and C_3-symmetric homohybrids derived from a series of mono- and diterpenes, steroids, and alkaloids have been reported. Both procedures are based on the mono-addition of bis(alkynyl) dilithium reagents to natural products bearing a carbonyl group to produce the corresponding alkynyl derivatives. Subjecting these alkynyl natural product mono-adducts to Glaser–Hay Cu-promoted homocoupling or the CuAAC reaction resulted in the synthesis of steroid-, terpene-, and alkaloid-based homohybrid derivatives incorporating diverse spacers to join the natural product scaffolds. The compatibility of both approaches with densely functionalized natural products, such as the highly sensitive diterpene 19-acetylgnaphalin, has also been studied. The use of ferrocenyl-bis(azide)s offers access to new bioorganometallic homohybrids having two steroidal, two diterpenic, or two alkaloid moieties tethered to the metallic nucleus through two triazole rings. Furthermore, straightforward entries to novel closed highly symmetrical and complex estrone-based macrocyclic and cage architectures by means of the Glaser–Eglinton homocoupling and the CuAAC protocol have been devised. The modular protocol developed here constitutes an excellent means of preparing structurally diverse steroid-based macro-



Scheme 13. Synthesis of estrone-derived cage **47**.

cycles and molecular cages. Investigations of the use of these molecular architectures in different supramolecular processes are underway in our laboratories.

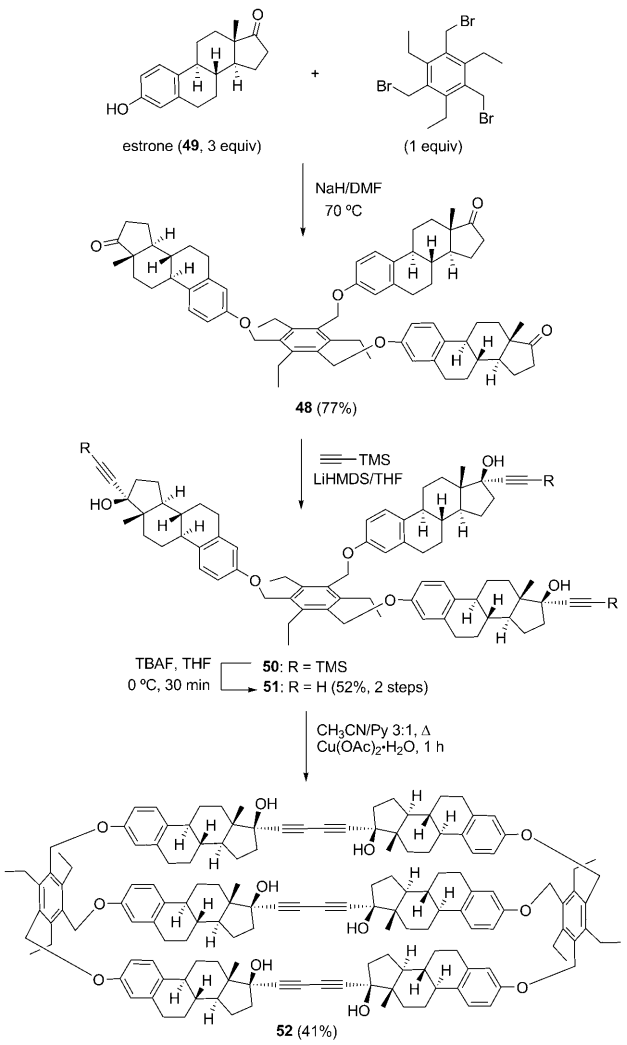
Experimental Section

General procedures: Flame-dried glassware and standard Schlenk techniques were used for moisture-sensitive reactions. DMF, MeCN, and THF were dried by passage through solvent-purification columns containing activated alumina. Other solvents were HPLC grade and were used without further purification. All reagents were obtained from commercial sources and were used without further purification, unless noted otherwise. Flash column chromatography was performed using silica gel (Merck, no. 9385, 230–400 mesh). Products were identified by means of TLC (60 F_{254}, Merck). UV light ($\lambda = 254$ nm) was used to develop the plates. ^{1}H and ^{13}C NMR spectra were recorded at 300, 400, or 500 MHz (^{1}H NMR) and at 75 or 100 MHz (^{13}C NMR) using $CDCl_3$ as solvent, with the residual solvent signal as the internal reference ($CHCl_3$/$CDCl_3$, $\delta = 7.25$ and 77.0 ppm). The following abbreviations are used to describe peak patterns when appropriate: s (singlet), d (doublet), t (triplet), q (quadruplet), m (multiplet), and br (broad). Mass spectra were recorded using the electron impact (EI) technique with an ionization energy of 70 eV, atmospheric pressure chemical ionization (APCI), matrix-assisted laser desorption/ionization (MALDI), or electrospray (ESI) chemical ionization techniques in positive mode, unless noted otherwise. IR spectra were obtained on a Perkin–Elmer 681 spectrophotometer. Optical rotations were measured on a 241 MC polarimeter using light from a sodium lamp. Melting points were determined on a Koffler block. Elemental analyses were performed with a Carlo Erba EA 1108 apparatus.

General procedure for the addition of aromatic bis(alkyne)s to natural products—synthesis of compounds 12–14, 16, and 17: Lithium bis(trimethylsilyl)amide (LiHMDS, 1.0 M in THF) was added dropwise to a solution of the appropriate aromatic bis(alkyne) in THF at −78 °C under argon. After stirring for 30 min, the resulting mixture was allowed to reach −50 °C and then a solution of the requisite natural product in THF was added via a cannula at the same temperature. The reaction mixture was stirred at the temperature specified below until completion of the reaction (TLC analysis). After quenching with saturated aqueous NH_4Cl solution and stirring for 30 min, the layers were separated. The aqueous layer was extracted twice with AcOEt. The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuo. Pure reaction products were obtained by chromatography on silica gel.

Compound 14: Following the general procedure, a solution of 3-*O*-methylestrone (**11**) (112 mg, 0.39 mmol) in THF (10 mL) was added to the organolithium reagent prepared from 1,3-diethynylbenzene (100 mg, 0.79 mmol) and LiHMDS (1.7 mL, 1.70 mmol, 1.0 M in THF) in THF (20 mL). The resulting mixture was stirred at −50 °C for 3 h. Chromatography on silica gel (hexanes/AcOEt 9:1) of the crude product obtained following the general work-up yielded 160 mg (99 %) of pure **14** as a yellow solid. M.p. 52–56 °C (amorphous); $[\alpha]_D^{20} = -32.71$ ($c = 0.61$ in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 7.58$ (br s, 1H; Ar), 7.43 (dd, $J = 7.9$, 1.3 Hz, 2H; Ar), 7.26 (m, 2H, H-1; Ar), 6.72 (dd, $J = 8.5$, 2.6 Hz, 1H; H-2), 6.64 (d, $J = 2.6$ Hz, 1H; H-4), 3.78 (s, 3H; OCH_3), 3.05 (s, 1H; C≡CH), 2.87 (m, 2H), 2.50–1.26 (m, 14H), 0.93 ppm (s, 3H; H-18); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 157.4$ (C; C-3), 137.9 (C; C-5), 135.0 (CH; Ar), 132.5 (C; C-10), 131.9 (CH; Ar), 131.7 (CH; Ar), 128.3 (CH; Ar), 126.3 (CH; C-1), 123.3 (C; Ar), 122.4 (C; Ar), 113.7 (CH; C-4), 111.5 (CH; C-2), 93.6 (C; C≡C), 84.9 (C; C≡C), 82.7 (C; C≡C), 80.2 (C; C-17), 77.8 (CH; C≡CH), 55.1 (OCH_3), 49.8 (CH; C-14), 47.6 (C; C-13), 43.6 (CH; C-9), 39.4 (CH; C-8), 39.0 (CH_2; C-16), 33.1 (CH_2; C-12), 29.8 (CH_2; C-6), 27.2 (CH_2; C-7), 26.4 (CH_2; C-11), 22.9 (CH_2; C-15), 12.9 ppm (CH_3; C-18); IR (KBr): $\tilde{\nu} =$ 3436, 3292, 2930, 1609, 1500, 1254, 895, 795 cm^{-1}; MS (EI): *m*/*z* (%): 410 $[M]^+$ (100), 395 (21), 316 (19), 284 (32), 267 (72), 242 (32), 227 (42), 174 (66), 147 (36), 126 (25), 115 (21), 91 (12); elemental analysis calcd (%) for $C_{29}H_{30}O_2$: C 84.84, H 7.37; found: C 85.02, H 7.08.

Compound 16 from 19-acetylgnaphalin (15) and lithium TMS-acetylide: *t*BuLi (0.17 mL, 0.28 mmol, 1.7 M in hexanes) was added to a solution of ethynyltrimethylsilane (42 μL, 0.30 mmol) in THF (5 mL) at −78 °C. After stirring for 30 min, a solution of 19-acetylgnaphalin (**26**) (100 mg, 0.25 mmol) in THF (5 mL) was added via a cannula. The reaction mixture was stirred for 30 min at −78 °C and then saturated aqueous NH_4Cl solution was added. The resulting mixture was extracted with AcOEt (3× 25 mL), and the combined layers were washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuo. Chromatography on silica gel (hexanes/AcOEt 7:3) of the crude product afforded 90 mg (72 %) of pure **16-TMS** as a white solid. M.p. 65–67 °C (amorphous); $[\alpha]_D^{20} = +31.16$ ($c = 0.52$ in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 7.42$ (m, 2H; H-15, H-16), 6.38 (dd, $J = 1.9$, 0.9 Hz, 1H; H-14), 5.35 (t, $J =$ 8.9 Hz, 1H; H-12), 5.10 (d, $J = 13.6$ Hz, 1H; H_B-19), 4.84 (d, $J = 13.6$ Hz, 1H; H_A-19), 4.69 (dd, $J = 3.6$, 2.3 Hz, 1H; H_B-18), 4.16 (s, 1H; OH), 2.42–2.10 (m, 7H), 2.07 (s, 3H; $COCH_3$), 2.00–1.55 (m, 4H), 1.52 (qt, $J =$ 13.1, 4.2 Hz, 1H), 1.04 (m overlapped, 1H), 1.02 (d, $J = 6.8$ Hz, 3H; H-17), 0.16 ppm (s, 9H; TMS); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 175.9$ (C=O; C-20), 170.4 (C; $COCH_3$), 144.1 (CH; C-15), 139.5 (CH; C-16), 125.0 (C; C-13), 109.7 (C; *C*≡C-Si), 107.9 (CH; C-14), 94.7 (C; C≡*C*-Si), 73.9 (C; C-6), 71.4 (CH; C-12), 64.9 (C; C-4), 62.9 (CH_2; C-19), 52.3 (CH_2; C-18), 51.3 (CH; C-10), 50.8 (C; C-9), 47.2 (C; C-5), 44.9 (CH_2; C-11), 41.0 (CH_2; C-7), 37.4 (CH; C-8), 32.9 (CH_2; C-3), 24.5 (CH_2; C-2), 23.4 (CH_2;



Scheme 14. Synthesis of hexameric estrone-based cage **52**.

C-1), 21.2 (CH_3; $COCH_3$), 15.8 (CH_3; C-17), 0.3 ppm ($3CH_3$; TMS); IR (KBr): $\tilde{\nu}$ = 3460, 2962, 2159, 1763, 1251, 1153, 1038, 925, 875, 844, 760 cm^{-1}; MS (EI): *m/z* (%): 500 $[M]^+$ (absent), 482 $[M-H_2O]^+$ (1), 458 (2), 440 (5), 425 (5), 409 (11), 303 (26), 273 (54), 255 (41), 167 (48), 123 (90), 95 (51), 73 (100).

Solid $nBu_4NF{\cdot}3H_2O$ (95 mg, 0.30 mmol) was added in portions to a solution of alkyne **16-TMS** (150 mg, 0.30 mmol) in THF (10 mL) at −78 °C under argon. The resulting mixture was stirred for 30 min at the same temperature. It was then filtered through a short pad of silica gel (AcOEt) and the solvents were removed in vacuo to yield **16** (116 mg, 90%) as a white solid. M.p. 169–170 °C; $[\alpha]_D^{30}$ = +28.24 (*c* = 1.42 in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.42 (m, 2H; H-15, H-16), 6.36 (dd, *J* = 1.5 Hz, 0.9 Hz, 1H; H-14), 5.34 (t, *J* = 8.7 Hz, 1H; H-12), 5.11 (d, *J* = 13.8 Hz, 1H; H_B-19), 4.81 (d, *J* = 13.8 Hz, 1H; H_A-19), 4.66 (dd, *J* = 3.3, 2.1 Hz, 1H; H-18), 4.23 (s, 1H; OH), 2.78 (s, 1H; C≡CH), 2.48–2.00 (m, 7H), 2.06 (s, 3H; $COCH_3$), 2.00 (m, 1H), 1.91 (m, 1H), 1.72 (dd, *J* = 13.8, 3.9 Hz, 1H), 1.70 (m, 1H), 1.56 (qt overlapped, *J* = 13.2, 4.4 Hz, 1H), 1.06 (m overlapped, 1H), 1.01 ppm (d, *J* = 6.6 Hz, 3H; H-17); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 176.0 (C=O; C-20), 170.4 (C; $COCH_3$), 144.1 (CH; C-15), 139.5 (CH; C-16), 125.0 (C; C-13), 107.9 (CH; C-14), 87.7 (C; C≡C), 78.0 (CH; C≡CH), 73.8 (C; C-6), 71.5 (CH; C-12), 65.0 (C; C-4), 63.0 (CH_2; C-19), 52.4 (CH_2; C-18), 51.4 (CH; C-10), 50.5 (C; C-9), 47.1 (C; C-5), 44.7 (CH_2; C-11), 41.3 (CH_2; C-7), 37.2 (CH; C-8), 32.9 (CH_2; C-3), 24.4 (CH_2; C-2), 23.4 (CH_2; C-1), 21.2 (CH_3; $COCH_3$), 15.8 ppm (CH_3; C-17); IR (film): $\tilde{\nu}$ = 3466, 2950, 2873, 1753, 1739, 1444, 1250, 1187, 1154, 1025, 922, 873, 808 cm^{-1}; MS (APCI): *m/z*: 429 $[M+H]^+$; elemental analysis calcd (%) for $C_{24}H_{28}O_7$: C 67.28, H 6.59; found: C 67.50, H 6.75.

General procedure for the Cu^I-catalyzed oxidative coupling of terminal alkynes—synthesis of compounds 21–26: CuCl (10 equiv) and freshly distilled TMEDA (10 equiv) were successively added to a solution of the appropriate alkyne (1 equiv) in dry CH_2Cl_2 at room temperature. The dark-green mixture was stirred at the same temperature under air until the starting material was no longer detected (TLC analysis). The reaction mixture was then partitioned between CH_2Cl_2 and H_2O. The organic layer was separated, washed with H_2O until it became colorless, dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuo. Chromatography on silica gel of the crude products afforded the desired pure compounds.

Dimer 23 by coupling of alkyne 14: Following the general procedure, dimer **23** was prepared from alkyne **14** (50 mg, 0.122 mmol), CuCl (121 mg, 1.22 mmol), and TMEDA (183 μL, 1.22 mmol) in dry CH_2Cl_2 (10 mL). The reaction mixture was stirred for 2 h at room temperature. Chromatography on silica gel (hexanes/AcOEt 9:1) of the crude product obtained following the general work-up yielded 44 mg (88%) of pure **23** as a yellow solid. M.p. 104–106 °C; $[\alpha]_D^{26}$ = −41.50 (*c* = 0.56 in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.59 (brs, 2H; Ar), 7.44 (dt, *J* = 7.9, 1.6 Hz, 4H; Ar), 7.28 (t, *J* = 7.9 Hz, 2H; Ar), 7.22 (d, *J* = 8.6 Hz, 2H; H-1), 6.72 (dd, *J* = 8.6, 2.5 Hz, 2H; H-2), 6.63 (d, *J* = 2.5 Hz, 2H; H-4), 3.78 (s, 6H; OCH_3), 2.86 (m, 4H), 2.40 (m, 4H), 2.30–1.30 (m, 24H), 0.93 ppm (s, 6H; H-18); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 157.4 (2C; C-3), 137.9 (2C; C-5), 135.4 (2CH; Ar), 132.4 (2C; C-10), 132.3 (2CH; Ar), 132.0 (2CH; Ar), 128.5 (2CH; Ar), 126.3 (2CH; C-1), 123.5 (2C; Ar), 121.9 (2C; Ar), 113.7 (2CH; C-4), 111.4 (2CH; C-2), 93.8 (2C; C≡C), 84.7 (2C; C≡C), 80.8 (2C; C-17), 80.2 (2C; C≡C), 74.3 (2C; C≡C), 55.1 ($2OCH_3$), 49.8 (2CH; C-14), 47.6 (2C; C-13), 43.6 (2CH; C-9), 39.4 (2CH; C-8), 39.0 ($2CH_2$; C-16), 33.0 ($2CH_2$; C-12), 29.8 ($2CH_2$; C-6), 27.2 ($2CH_2$; C-7), 26.4 ($2CH_2$; C-11), 22.9 ($2CH_2$; C-15), 12.8 ppm ($2CH_3$; C-18); IR (KBr): $\tilde{\nu}$ = 3460, 2930, 2865, 1610, 1591, 1499, 1254, 1041, 793, 684 cm^{-1}; MS (ESI): *m/z*: 818.3 $[M]^+$ (absent), 783 $[M-2H_2O+H]^+$; elemental analysis calcd (%) for $C_{58}H_{58}O_4$: C 85.05, H 7.14; found: C 84.73, H 7.38.

Dimer 24 by coupling of alkyne 17: Following the general procedure, dimer **24** was prepared from alkyne **17** (50 mg, 0.095 mmol), CuCl (94 mg, 0.95 mmol), and TMEDA (142 μL, 0.95 mmol) in dry CH_2Cl_2 (10 mL). The reaction mixture was stirred for 2 h at room temperature. Chromatography on silica gel (hexanes/AcOEt3:2) of the crude product obtained following the general work-up yielded 44 mg (88%) of pure **24** as a white solid. M.p. 125–127 °C; $[\alpha]_D^{26}$ = +80.54 (*c* = 0.44 in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.52 (m, 2H; Ar), 7.48 (dt, *J* = 8.6, 1.3 Hz, 2H; Ar), 7.43 (m, 2H; Ar), 7.41 (m, 2H; Ar), 7.40 (dt, *J* = 7.9, 1.4 Hz, 2H; Ar), 7.32 (t, *J* = 7.7 Hz, 2H; Ar), 6.37 (dd, *J* = 1.8, 0.9 Hz, 2H; H-14), 5.37 (t, *J* = 8.6 Hz, 2H; H-12), 5.16 (d, *J* = 13.7 Hz, 2H; H_B-19), 4.86 (d, *J* = 13.7 Hz, 2H; H_A-19), 4.62 (dd, *J* = 3.6, 2.2 Hz, 2H; H_B-18), 4.28 (s, 2H; OH), 2.58–2.16 (overlapped, 14H), 2.08 (s, 6H; $COCH_3$), 2.04 (m, 2H), 1.92 (m, 2H), 1.81 (dd, *J* = 13.9, 4.5 Hz, 2H), 1.75 (qd overlapped, *J* = 13.2, 3.9 Hz, 2H), 1.56 (qt, *J* = 13.4, 4.0 Hz, 2H), 1.07 (overlapped, 2H), 1.04 ppm (d, *J* = 6.8 Hz, 6H; H-17); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 175.9 (2C; C-20), 170.5 (2C; $COCH_3$), 144.2 (2CH; C-15), 139.5 (2CH; C-16), 134.9 (2CH; Ar), 132.5 (2CH; Ar), 132.0 (2CH; Ar), 128.8 (2CH; Ar), 125.0 (2C; C-13), 122.9 (2C; Ar), 122.0 (2C; Ar), 107.9 (2CH; C-14), 94.2 (2C; C≡C), 88.1 (2C; C≡C), 80.8 (2C; C≡C), 74.4 (2C; C≡C), 74.3 (2C; C-6), 71.5 (2CH; C-12), 65.1 (2C; C-4), 63.0 ($2CH_2$; C-19), 52.3 ($2CH_2$; C-18), 51.4 (2CH; C-10), 50.9 (2C; C-9), 47.6 (2C; C-5), 44.9 ($2CH_2$; C-11), 41.4 ($2CH_2$; C-7), 37.6 (2CH; C-8), 32.9 ($2CH_2$; C-3), 24.5 ($2CH_2$; C-2), 23.4 ($2CH_2$; C-1), 21.3 ($2CH_3$; $COCH_3$), 15.9 ppm ($2CH_3$; C-17); IR (KBr): $\tilde{\nu}$ = 3454, 2964, 2932, 2877, 2215, 1762, 1737, 1633, 1590, 1250, 1153, 1045, 925, 875, 796 cm^{-1}; MS (ESI): *m/z*: 1077.3 $[M+Na]^+$; elemental analysis calcd (%) for $C_{64}H_{62}O_{14}$: C 72.85, H 5.92; found: C 73.19, H 5.66.

Dimer 25 by coupling of alkyne 19: Following the general procedure, dimer **25** was prepared from alkyne **19** (30 mg, 0.046 mmol), CuCl

(46 mg, 0.46 mmol), and TMEDA (69 μL, 0.46 mmol) in dry CH_2Cl_2 (10 mL). The reaction mixture was stirred for 5 h at room temperature. Chromatography on silica gel (hexanes/AcOEt 1:1) of the crude product obtained following the general work-up yielded 18 mg (61%) of pure **25** as an orange solid. M.p. 178–180 °C; $[\alpha]_D^{20} = -261.06$ ($c = 0.32$ in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 7.35$ (d, $J = 8.2$ Hz, 2H; H-9), 7.32 (s, 4H; H-25, H-29), 7.24 (d, $J = 2.3$ Hz, 2H; H-12), 6.81 (dd, $J = 8.2$, 2.3 Hz, 2H; H-10), 5.03 (ddd, $J = 11.9$, 9.6, 5.1 Hz, 2H; H-18), 4.05 (br s, 2H; H-3), 3.92 (s, 18H; OMe-30, OMe-32, OMe-31), 3.90 (m overlapped, 2H; H-17), 3.87 (s, 6H; OMe-35), 3.83 (s, 6H; OMe-34), 3.52 (s, 6H; OMe-33), 3.26 (t, $J = 12.8$ Hz, 2H; H-21), 3.00 (m, 2H; H-15), 2.96 (d, $J = 16.7$ Hz, 2H; $CH_2C{\equiv}C$), 2.75 (dd, $J = 10.9$, 4.7 Hz, 2H; H-16), 2.69 (dd, $J = 14.0$, 2.7 Hz, 2H; H-21), 2.62 (dd, $J = 11.7$, 2.7 Hz, 2H; H-5), 2.40–2.00 (overlapped, 12H), 1.95 (br d overlapped, 2H; H-20), 1.90 (m, 2H; H-19), 1.82 ppm (m, 2H; H-6); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 182.8$ (2C; C-2), 172.6 (2C; C-22), 165.4 (2C; C-23), 160.3 (2C; C-11), 155.3 (2C; C-13), 152.9 (4C; C-26, C-28), 142.2 (2C; C-27), 135.3 (2C; C-8), 125.4 (2C; C-24), 122.6 (2CH; C-9), 111.7 (2CH; C-10), 106.7 (4CH; C-25, C-29), 106.6 (2CH; C-12), 78.0 (2CH; C-18), 77.9 (2CH; C-17), 73.4 (2C; $C{\equiv}C$), 67.6 (2C; $C{\equiv}C$), 60.9 ($2OCH_3$; C-31), 60.8 ($2OCH_3$; C-33), 56.2 ($4OCH_3$; C-30, C-32), 55.5 ($2OCH_3$; C-35), 54.7 (2CH; C-3), 54.6 (2C; C-7), 52.0 ($2OCH_3$; C-34), 51.9 (2CH; C-16), 50.4 ($2CH_2$; C-5), 49.3 ($2CH_2$; C-21), 34.5 (2CH; C-20), 33.3 ($2CH_2$; C-6), 31.2 (2CH; C-15), 29.6 ($2CH_2$; C-19), 24.4 ($2CH_2$; $CH_2C{\equiv}C$), 22.6 ppm ($2CH_2$; C-14); IR (KBr): $\tilde{\nu} = 3436$, 2832, 1735, 1713, 1589, 1462, 1416, 1335, 1250, 1226, 1128, 1106, 982, 762 cm^{-1}; MS (APCI): m/z: 1291 $[M+H]^+$; elemental analysis calcd (%) for $C_{72}H_{82}N_4O_{18}$: C 66.96, H 6.40, N 4.34; found: C 66.63, H 6.71, N 4.66.

General procedure for the synthesis of oligomers 29a–c, 30a,b, 31, 32a,b, 33, 36, 37, 40ab, 40bc, 40cc, 40cd, 45a–c, and 47: A mixture of the requisite organic azide (1.0 equiv), the requisite alkyne (1.0 equiv per equiv of N_3), sodium L-ascorbate (0.10–2.00 equiv), and $CuSO_4{\cdot}5H_2O$ (0.05–1.00 equiv) in DMF was stirred under Ar at RT for the period of time specified below. The reaction was then quenched with water at 0 °C (slightly exothermic) and the mixture was allowed to reach RT. It was then extracted with AcOEt (three times) and the combined organic extracts were washed twice with water and once with brine. The organic layer was dried over $MgSO_4$ and filtered, and the solvent was removed in vacuo to afford the respective reaction product, which was purified by passage through a short pad of SiO_2.

Compound 29b: Reaction of a mixture of diazide **28b** (28 mg, 0.090 mmol, 1.0 equiv), mestranol (**27**) (56 mg, 0.180 mmol, 2.0 equiv), sodium L-ascorbate (11 mg, 0.054 mmol, 0.6 equiv), and $CuSO_4{\cdot}5H_2O$ (7 mg, 0.027 mmol, 0.3 equiv) in DMF (4 mL) for 6.5 h, followed by purification (SiO_2; AcOEt to AcOEt/MeOH 9:1), yielded pure **29b** as an orange solid (75 mg, 90%). M.p. 190 °C (decomp.); $[\alpha]_D^{20} = +18.63$ ($c = 0.26$ in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 7.40$ (s, 2H; $N_3C{=}CH$), 7.12 (d, $J = 8.4$ Hz, 2H; H-1), 6.67 (dd, $J = 8.4$, 2.1 Hz, 2H; H-2), 6.61 (d, $J = 2.1$ Hz, 2H; H-4), 5.19 (s, 4H; CH_2N_3), 4.26 (s, 4H; Cp), 4.22 (s, 4H; Cp), 3.76 (s, 6H; OCH_3), 2.85 (m, 4H), 2.40–1.20 (m, 28H), 1.04 ppm (s, 6H; C-18); ^{13}C NMR (75 MHz, [D$_6$]DMSO): $\delta = 156.8$ (2C; C-3), 154.0 (2C; $N_3C{=}CH$), 137.3 (2C; C-5), 132.0 (2C; C-10), 126.0 (2CH; C-1), 122.1 (2CH; $N_3C{=}CH$), 113.3 (2CH; C-4), 111.3 (2CH; C-2), 83.3 (2C; Cp), 81.0 (2C; C-17), 69.4 (4CH; Cp), 69.1 (4CH; Cp), 54.7 ($2OCH_3$), 48.3 ($2CH_2$; CH_2N_3), 47.5 (2CH; C-14), 46.5 (2C; C-13), 43.1 (2CH; C-9), 39.7 (2CH; C-8), 37.1 ($2CH_2$; C-16), 32.5 ($2CH_2$; C-12), 29.2 ($2CH_2$; C-6), 27.0 ($2CH_2$; C-7), 25.9 ($2CH_2$; C-11), 23.4 ($2CH_2$; C-15), 14.3 ppm ($2CH_3$; C-18); IR (KBr): $\tilde{\nu} = 3414$, 2932, 2863, 1611, 1501, 1452, 1289, 1254, 1238, 1142, 1105, 1041, 843, 814, 491 cm^{-1}; MS (ESI): m/z: 917 $[M+H]^+$; elemental analysis calcd (%) for $C_{54}H_{64}FeN_6O_4$: C 70.73, H 7.03, N 9.17; found: C 70.50, H 6.90, N 8.93.

Compound 30b: Reaction of a mixture of diazide **28b** (15 mg, 0.051 mmol, 1.0 equiv), alkyne **20** (68 mg, 0.105 mmol, 2.1 equiv), sodium L-ascorbate (6 mg, 0.030 mmol, 0.6 equiv), and $CuSO_4{\cdot}5H_2O$ (4 mg, 0.015 mmol, 0.3 equiv) in DMF (4 mL) for 3 h, followed by purification (SiO_2; hexanes/AcOEt 3:7 to AcOEt/MeOH 9:1), yielded pure **30b** as an orange solid (65 mg, 80%). M.p. 142–144 °C (amorphous); $[\alpha]_D^{20} = -90.23$ ($c = 0.35$ in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 7.32$ (overlapped, 6H; H-9, H-25, H-29), 7.28 (s, 2H; $N_3C{=}CH$), 6.96 (br s, 2H; H-12), 6.74 (d, $J = 8.4$ Hz, 2H; H-10), 5.37 (d, $J = 17.2$ Hz, 2H; $CHHC{=}CN_3$), 5.16 (d, $J = 17.2$ Hz, 2H; $CHHC{=}CN_3$), 5.10 (d, $J = 2.4$ Hz, 4H; CH_2N_3), 5.02 (br dd, $J = 11.4$, 4.8 Hz, 2H; H-18), 4.19 (br s, 2H; H-3), 4.07–4.04 (m overlapped, 8H; Cp), 3.92 (s, 18H; OMe-30, OMe-32, OMe-31), 3.88–3.84 (m, 2H; H-17), 3.77 (s, 6H; OMe-35), 3.72 (s, 6H; OMe-34), 3.49 (s, 6H; OMe-33), 3.16 (m overlapped, 6H; 2H-5, H-21), 2.94 (d, $J = 8.7$ Hz, 2H; H-6), 2.68 (d, $J = 10.7$ Hz, 2H; H-16), 2.47 (br m, 2H; H-6), 2.38 (m overlapped, 8H; H-21, H-19, 2H-14), 2.21 (m overlapped, 2H; H-15), 2.01 (m, 2H; H-19), 1.98 ppm (m, 2H; H-20); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 172.3$ (2C=O; C-22), 165.3 (2C=O; C-23), 156.5 (2C; C-11), 152.9 (4C; C-28, C-26), 144.8 (2C; $N_3C{=}CH$), 142.2 (2C; C-27), 138.2 (2C; C-13), 132.1 (2C; C-2), 125.3 (2C; C-24), 121.6 (2C; C-8), 121.0 (2CH; $N_3C{=}CH$), 118.6 (2CH; C-9), 109.9 (2C; C-7), 109.0 (2CH; C-10), 106.7 (4CH; C-25, C-29), 93.7 (2CH; C-12), 82.1 (2C; Cp), 77.8 (2CH; C-17), 77.6 (2CH; C-18), 69.7 (4CH; Cp), 69.4 (2CH; Cp), 69.3 (2CH; Cp), 60.8 ($2OCH_3$; C-31), 60.6 ($2OCH_3$; C-33), 56.2 ($4OCH_3$; C-30, C-32), 55.8 ($2OCH_3$; C-35), 55.3 (2CH; C-3), 51.9 ($2OCH_3$ + 2CH; C-16, C-34), 51.4 ($2CH_2$; C-5), 50.6 ($2CH_2$; CH_2N_3), 49.4 ($2CH_2$; C-21), 40.7 ($2CH_2$; $CH_2C{=}CN_3$), 33.6 (2CH; C-20), 32.4 (2CH; C-15), 30.6 ($2CH_2$; C-19), 25.4 ($2CH_2$; C-14), 17.9 ppm ($2CH_2$; C-6); IR (KBr): $\tilde{\nu} = 3435$, 2936, 2837, 1716, 1622, 1589, 1504, 1493, 1458, 1415, 1333, 1255, 1224, 1179, 1154, 1127, 1043, 762 cm^{-1}; MS (ESI): m/z: 1589 $[M+H]^+$; elemental analysis calcd (%) for $C_{84}H_{96}FeN_{10}O_{18}$: C 63.47, H 6.09, N 8.81; found: C 63.70, H 5.77, N 8.55.

Compound 31: Reaction of a mixture of diazide **28a** (11.0 mg, 0.052 mmol, 1.0 equiv), alkyne **19** (67.3 mg, 0.104 mmol, 2.0 equiv), sodium L-ascorbate (2.0 mg, 0.010 mmol, 0.2 equiv), and $CuSO_4{\cdot}5H_2O$ (1.2 mg, 0.005 mmol, 0.1 equiv) in DMF (3 mL) for 1 h, followed by purification (SiO_2; AcOEt to AcOEt/MeOH 9:1), yielded pure **31** as a yellow solid (59 mg, 75%). M.p. 150–153 °C; $[\alpha]_D^{25} = -119.20$ ($c = 0.60$ in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 7.32$ (s, 6H; H-9, H-25, H-29), 7.12 (s, 2H; $N_3C{=}CH$), 7.09 (d, $J = 2.4$ Hz, 2H; H-12), 6.73 (dd, $J = 8.1$, 2.4 Hz, 2H; H-10), 6.34 (s, 4H; $CH_2C{=}CN_3$), 5.01 (m, 2H; H-18), 4.36 (d, $J = 5.1$ Hz; 2H), 4.16 (d, $J = 14.1$ Hz, 2H; $CHHN_3$), 4.06 (d, $J = 14.1$ Hz, 2H; $CHHN_3$), 3.93 (s, 18H; OCH_3-30, OCH_3-31, OCH_3-32), 3.92 (m overlapped, 4H; H-17, H-3), 3.81 (s, 6H; OCH_3-35), 3.76 (s, 6H; OCH_3-34), 3.56–3.46 (m overlapped, 2H), 3.51 (s, 6H; OCH_3-33), 3.13 (d, $J = 14.6$ Hz, 2H; H-21), 2.92 (m, 2H; H-15), 2.68 (m, 6H; H-21, H-16, H-5), 2.35–2.00 (m, 6H; H-5, 2H-14), 1.98–1.78 (m, 8H; H-20, H-19, H-6), 1.00 ppm (s, 6H; $O_2C(CH_3)_2$); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 184.1$ (2C; C-2), 172.4 (2C=O; C-22), 165.4 (2C=O; C-23), 160.2 (2C; C-11), 155.5 (2C; C-13), 152.9 (4C; C-26, C-28), 142.3 (2C; $N_3C{=}CH$), 142.2 (2C; C-27), 135.5 (2C; C-8), 125.4 (2C; C-24), 122.8 (2CH; C-9), 121.7 (2CH; $N_3C{=}CH$), 111.5 (2CH; C-10), 109.7 (C; $O_2C(CH_3)_2$), 106.7 (4CH; C-25, C-29), 106.4 (2CH; C-12), 78.1 (2CH; C-18), 77.9 (2CH; C-17), 74.5 (2CH; $OCHCH_2N_3$), 60.8 ($2OCH_3$; C-31), 60.7 ($2OCH_3$; C-33), 56.8 (2CH; C-3), 56.2 ($4OCH_3$; C-30, C-32), 55.5 ($2OCH_3$, C-35), 54.9 (2C; C-7), 52.1 ($2CH_3$; C-34), 51.7 (2CH; C-16), 50.2 ($2CH_2$; C-5), 49.5 ($2CH_2$; CH_2N_3), 49.2 ($2CH_2$; C-21), 35.7 ($2CH_2$; C-6), 34.6 (2CH; C-20), 31.3 (2CH; C-15), 30.3 ($2CH_2$; $CH_2C{=}CN_3$), 29.6 ($2CH_2$; C-19), 26.5 ($2CH_3$; $O_2C(CH_3)_2$), 22.4 ppm ($2CH_2$; C-14); IR (KBr): $\tilde{\nu} = 3435$, 2938, 2837, 1736, 1716, 1619, 1589, 1504, 1482, 1462, 1416, 1374, 1335, 1301, 1277, 1251, 1225, 1178, 1128, 1107, 1044, 1029, 998, 983, 763 cm^{-1}; MS (ESI): m/z: 1506.2 $[M+H]^+$; elemental analysis calcd (%) for $C_{79}H_{96}N_{10}O_{20}$: C 63.02, H 6.43, N 9.30; found: C 63.33, H 6.21, N 9.15.

Compound 33: Reaction of a mixture of diazide **28a** (11 mg, 0.054 mmol, 1.0 equiv), alkyne **17** (60 mg, 0.114 mmol, 2.1 equiv), sodium L-ascorbate (2 mg, 0.011 mmol, 0.2 equiv), and $CuSO_4{\cdot}5H_2O$ (1 mg, 0.005 mmol, 0.1 equiv) in DMF (4 mL) for 1.5 h, followed by purification (SiO_2; hexanes/AcOEt 1:1 to AcOEt), yielded pure **33** as a white solid (62 mg, 90%). M.p. 187–190 °C; $[\alpha]_D^{30} = +40.39$ ($c = 1.03$ in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 7.94$ (s, 2H; $N_3C{=}CH$), 7.75 (m, 2H; Ar), 7.44–7.38 (m, 10H; H-16, H-15, Ar), 6.38 (br s, 2H; H-14), 5.38 (t, $J = 8.4$ Hz, 2H; H-12), 5.18 (d, $J = 13.5$ Hz, 2H; H_B-19), 4.88 (d, $J = 13.5$ Hz, 2H; H_A-19), 4.71 (br s, 2H; H-18), 4.66 (br s, 4H; CH_2N_3), 4.31 (s, 2H; OH), 4.12 (br s, 2H; OCHC), 2.60–2.20 (m, 14H), 2.11 (s, 6H; $COCH_3$), 2.00–1.50 (m, 10H), 1.25 (s, 6H; $O_2C(CH_3)_2$), 1.10 (m overlapped, 2H), 1.06 ppm (d, $J = 6.6$ Hz, 6H; H-17); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta =$

176.0 (2C=O; C-20), 170.5 (2C; $COCH_3$), 146.9 (2C; N_3C=CH), 144.1 (2CH; C-15), 139.5 (2CH; C-16), 131.1 (2CH; Ar), 130.7 (2C; Ar), 129.0 (2CH; Ar), 128.2 (2CH; Ar), 125.9 (2CH; N_3C=CH), 125.0 (2C; C-13), 123.0 (2C; Ar), 121.8 (2CH; Ar), 110.5 (C; $O_2C(CH_3)_2$), 108.0 (2CH; C-14), 93.5 (2C; C≡C), 89.0 (2C; C≡C), 75.4 (2CH; $OCHCH_2N_3$), 74.3 (2C; C-6), 71.5 (2CH; C-12), 65.1 (2C; C-4), 63.1 ($2CH_2$; C-19), 52.4 ($2CH_2$; C-18), 51.5 (2CH; C-10), 50.8 ($2CH_2$; CH_2N_3), 50.2 (2C; C-9), 47.6 (2C; C-5), 44.8 ($2CH_2$; C-11), 41.4 ($2CH_2$; C-7), 37.5 (2CH; C-8), 33.0 ($2CH_2$; C-3), 26.7 ($2CH_3$; $O_2C(CH_3)_2$), 24.4 ($2CH_2$; C-2), 23.4 ($2CH_2$; C-1), 21.3 ($2CH_3$; $COCH_3$), 16.0 ppm ($2CH_3$; C-17); IR (KBr): $\tilde{\nu}$=3454, 2965, 2879, 1762, 1738, 1609, 1458, 1368, 1250, 1180, 1153, 1113, 1043, 924, 875, 795, 601 cm^{-1}; MS (ESI): *m/z*: 1291.3 $[M+Na]^+$, 1269.6 $[M+H]^+$; elemental analysis calcd (%) for $C_{71}H_{76}N_6O_{16}$: C 67.18, H 6.03, N 6.62; found: C 66.95, H 5.84, N 6.38.

Compound 36: Reaction of a mixture of triazide **34a** (28.0 mg, 0.115 mmol, 1.0 equiv), mestranol (**27**) (107.1 mg, 0.345 mmol, 3.0 equiv), sodium L-ascorbate (6.9 mg, 0.035 mmol, 0.30 equiv), and $CuSO_4{\cdot}5H_2O$ (4.5 mg, 0.018 mmol, 0.15 equiv) in DMF (4 mL) for 1 h, followed by purification (SiO_2; hexanes/AcOEt 1:1 to AcOEt), yielded pure **36** as a white solid (125.0 mg, 93%). M.p. 179–181 °C; $[\alpha]_D^{25}$=+37.07 (*c*=0.74 in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ=7.36 (s, 3H; N_3C=CH), 7.12 (d, *J*=8.7 Hz, 3H; H-1), 7.08 (s, 3H; Ar), 6.66 (dd, *J*=8.7, 2.7 Hz, 3H; H-2), 6.61 (d, *J*=2.7 Hz, 3H; H-4), 5.49 (s, 6H; CH_2N_3), 3.75 (s, 9H; OCH_3), 2.92 (br s, 3H; OH), 2.88–2.83 (m, 6H), 2.44–2.34 (m, 3H), 2.20–2.05 (m, 6H), 2.01–1.90 (m, 9H), 1.62–1.33 (m, 18H), 1.03 (s, 9H; H-18), 0.68 ppm (td, *J*=12.9, 3.9 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ=157.4 (3C; C-3), 154.5 (3C; N_3C=CH), 138.0 (3C; Ar), 137.0 (3C; C-5), 132.5 (3C; C-10), 127.0 (3CH; Ar), 126.2 (3CH; C-1), 121.5 (3CH; N_3C=CH), 113.8 (3CH; C-4), 111.4 (3CH; C-2), 82.4 (3C; C-17), 55.2 ($3OCH_3$), 53.3 ($3CH_2$; CH_2N_3), 48.4 (3CH; C-14), 47.3 (3C; C-13), 43.4 (3CH; C-9), 39.4 (3CH; C-8), 37.9 ($3CH_2$; C-16), 33.0 ($3CH_2$; C-12), 29.8 ($3CH_2$; C-6), 27.4 ($3CH_2$; C-7), 26.2 ($3CH_2$; C-11), 23.5 ($3CH_2$; C-15), 14.2 ppm ($3CH_3$; C-18); IR (KBr): $\tilde{\nu}$=3436, 3133, 2930, 2867, 1610, 1576, 1500, 1454, 1255, 1235, 1129, 1043 cm^{-1}; MS (ESI): *m/z*: 1196.6 $[M+Na]^+$, 1120.3 $[M-3H_2O+H]^+$; elemental analysis calcd (%) for $C_{72}H_{87}N_9O_6$: C 73.63, H 7.47, N 10.73; found: C 73.29, H 7.28, N 10.48.

Compound 37: Reaction of a mixture of tetraazide **35** (17.6 mg, 0.059 mmol, 1.0 equiv), mestranol (**27**) (72.3 mg, 0.236 mmol, 4.0 equiv), sodium L-ascorbate (4.8 mg, 0.024 mmol, 0.4 equiv), and $CuSO_4{\cdot}5H_2O$ (3.0 mg, 0.012 mmol, 0.2 equiv) in DMF (3 mL) for 1 h, followed by purification (SiO_2; hexanes/AcOEt 1:1 to AcOEt), yielded pure **37** as a white solid (86.3 mg, 95%). M.p. 201–203 °C; $[\alpha]_D^{25}$=+44.90 (*c*=1.02 in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ=7.28 (s, 4H; N_3C=CH), 7.16 (s, 2H; Ar), 7.10 (d, *J*=8.5 Hz, 4H; H-1), 6.66 (dd, *J*=8.5, 2.7 Hz, 4H; H-2), 6.60 (d, *J*=2.7 Hz, 4H; H-4), 5.69 (d, *J*=15.0 Hz, 4H; C*H*HN_3), 5.52 (d, *J*=15.0 Hz, 4H; CH*H*N_3), 3.75 (s, 12H; OCH_3), 2.83–2.82 (m, 12H), 2.45 (m, 4H), 2.17–1.96 (m, 20H), 1.63–1.27 (m, 24H), 1.02 (s, 12H; H-18), 0.66 ppm (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$): δ=157.3 (4C; C-3), 154.6 (4C; N_3C=CH), 137.9 (4C; C-5), 134.7 (4C; Ar), 132.4 (4C; C-10), 131.7 (2CH; Ar), 126.1 (4CH; C-1), 122.1 (4CH; N_3C=CH), 113.7 (4CH; C-4), 111.3 (4CH; C-2), 82.3 (4C; C-17), 55.1 ($4OCH_3$), 50.4 ($4CH_2$; CH_2N_3), 48.3 (4CH; C-14), 47.2 (4C; C-13), 43.2 (4CH; C-9), 39.4 (4CH; C-8), 37.8 ($4CH_2$; C-16), 33.0 ($4CH_2$; C-12), 29.7 ($4CH_2$; C-6), 27.3 ($4CH_2$; C-7), 26.2 ($4CH_2$; C-11), 23.5 ($4CH_2$; C-15), 14.2 ppm ($4CH_3$; C-18); IR (KBr): $\tilde{\nu}$=3436, 2930, 2867, 1610, 1576, 1500, 1454, 1254, 1232, 1143, 1042 cm^{-1}; MS (ESI): *m/z*: 1562.8 $[M+Na]^+$; elemental analysis calcd (%) for $C_{94}H_{114}N_{12}O_8$: C 73.31, H 7.46, N 10.91; found: C 73.15, H 7.67, N 10.72.

Compound 40ab: A mixture of diazide **28b** (17.2 mg, 0.058 mmol, 1.0 equiv), bis(alkyne) **39a** (51.1 mg, 0.058 mmol, 1.0 equiv), sodium L-ascorbate (23.0 mg, 0.116 mmol, 2.0 equiv), and $CuSO_4{\cdot}5H_2O$ (7.2 mg, 0.029 mmol, 0.5 equiv) in DMF (80 mL) was stirred under Ar at RT for 3 days. The reaction was then quenched with water, the resulting mixture was extracted with AcOEt (100 mL), and the organic extracts were washed with water (2×100 mL) and brine (1×100 mL). The organic layer was dried over $MgSO_4$, filtered, and the solvent was removed in vacuo. The resulting yellow solid was purified by passage through a short pad of SiO_2 (6×1.5 cm, hexane/AcOEt 1:3 to AcOEt/MeOH 200:1) to afford **40ab** as a yellow solid (28.7 mg, 42%). M.p. 193–195 °C; $[\alpha]_D^{27}$=+10.45 (*c*=0.44 in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ=7.55 (s, 2H; N_3C=CH), 7.45 (s, 2H; N_3C=CH), 7.01 (d, *J*=8.4 Hz, 2H; H-1), 6.68–6.64 (m, 4H; H-2 + H-4), 5.30–5.17 (m, 8H), 4.51 (d, *J*=14.4 Hz, 2H), 4.40 (d, *J*=14.4 Hz, 2H), 4.20 (s, 6H; Cp), 4.13 (s, 2H; Cp), 3.88 (m, 2H; OCH), 2.77 (m, 4H), 2.37 (m, 2H), 2.08 (m, 4H), 1.90 (m, 6H), 1.64–1.25 (m, 14H), 1.01 (s, 6H), 0.98 (s, 6H), 0.68 ppm (br t, *J*=12.0 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ=155.6 (2C; C-3), 153.8 (2C; N_3C=CH), 145.1 (2C; N_3C=CH), 138.0 (2C; C-5), 133.0 (2C; C-10), 126.3 (2CH; C-1), 124.2 (2CH; N_3C=CH), 121.2 (2CH; N_3C=CH), 115.1 (2CH; C-4), 112.2 (2CH; C-2), 110.3 (2C; $O_2C(CH_3)_2$), 83.2 (2C; Cp), 82.4 (2C; C-17), 75.2 (2CH; OCH), 69.5 (4CH; Cp), 69.2 (2CH; Cp), 69.0 (2CH; Cp), 61.7 ($2CH_2$), 49.9 ($2CH_2$), 49.3 ($2CH_2$), 48.6 (2CH; C-14), 47.3 (2C; C-13), 43.5 (2CH; C-9), 39.4 (2CH; C-8), 38.1 ($2CH_2$; C-16), 33.0 ($2CH_2$; C-12), 29.8 ($2CH_2$; C-6), 27.3 ($2CH_2$; C-7), 26.4 ($2CH_3$), 26.3 ($2CH_2$; C-11), 23.4 ($2CH_2$; C-15), 14.2 ppm ($2CH_3$; C-18); IR (KBr): $\tilde{\nu}$=3436, 2929, 1609, 1497, 1456, 1381, 1232, 1049, 815 cm^{-1}; MS (ES): *m/z*: 1177.9 $[M+H]^+$; elemental analysis calcd (%) for $C_{65}H_{76}FeN_{12}O_6$ (%): C 66.32, H 6.51, N 14.28; found: C 66.54, H 6.78, N 14.42.

Dimer 42 by coupling of alkyne 38:[10] Following the general procedure, dimer **42** was prepared from alkyne **38** (200 mg, 0.492 mmol), CuCl (487 mg, 4.92 mmol), and TMEDA (0.74 mL, 4.92 mmol) in dry CH_2Cl_2 (10 mL). The reaction mixture was stirred for 16 h at room temperature. Chromatography on silica gel (hexanes/AcOEt 9:1) of the crude product obtained following the general work-up yielded 178 mg (89%) of pure **42** as a white solid. M.p. 88–90 °C; $[\alpha]_D^{26}$=−16.80 (*c*=0.36 in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ=7.24 (d, *J*=8.5 Hz, 2H; H-1), 6.74 (dd, *J*=8.5, 2.5 Hz, 2H; H-2), 6.66 (d, *J*=2.5 Hz, 2H; H-4), 4.72 (s, 4H; OCH_2), 2.82 (m, 4H), 2.40–1.20 (m, 28H), 0.87 (s, 6H; H-18), 0.19 ppm (s, 18H; TMS); ^{13}C NMR (75 MHz, $CDCl_3$): δ=155.3 (2C; C-3), 138.1 (2C; C-5), 133.7 (2C; C-10), 126.4 (2CH; C-1), 114.9 (2CH; C-4), 112.2 (2CH; C-2), 109.4 (2C; C≡C), 90.1 (2C; C≡C), 80.1 (2C; C-17), 74.8 (2C; C≡C), 70.9 (2C; C≡C), 56.2 ($2OCH_2$), 49.6 (2CH; C-14), 47.2 (2C; C-13), 43.7 (2CH; C-9), 39.3 (2CH; C-8), 38.9 ($2CH_2$; C-16), 32.8 ($2CH_2$; C-12), 29.8 ($2CH_2$; C-6), 27.2 ($2CH_2$; C-7), 26.4 ($2CH_2$; C-11), 22.8 ($2CH_2$; C-15), 12.7 ($2CH_3$; C-18), 0.00 ppm ($6CH_3$; TMS); IR (KBr): $\tilde{\nu}$=3437, 2932, 2865, 2159, 1608, 1497, 1249, 1029, 889, 843, 760 cm^{-1}; MS (APCI): *m/z*: 793 $[M-H_2O+H]^+$, 775 $[M-2H_2O+H]^+$.

Desilylation of compound 42 to afford 43: Solid nBu$_4$NF·3H$_2$O (151 mg, 0.48 mmol) was added to a solution of **42** (178 mg, 0.22 mmol) in THF (10 mL) at room temperature under argon. The resulting solution was stirred for 10 min until completion of the reaction (TLC analysis). The reaction mixture was then filtered through a short pad of silica gel using CH_2Cl_2 as eluent. Chromatography on silica gel (hexanes/AcOEt 4:1) of the residue obtained afforded 103 mg (70%) of pure **43** as a white solid. M.p. 128–130 °C; $[\alpha]_D^{20}$=+4.73 (*c*=0.34 in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ=7.22 (d, *J*=8.5 Hz, 2H; H-1), 6.74 (dd, *J*=8.5, 2.7 Hz, 2H; H-2), 6.66 (d, *J*=2.7 Hz, 2H; H-4), 4.71 (s, 4H; OCH_2), 2.84 (m, 4H), 2.61 (s, 2H; C≡CH), 2.40–1.25 (m, 28H), 0.88 ppm (s, 6H; H-18); ^{13}C NMR (75 MHz, $CDCl_3$): δ=155.2 (2C; C-3), 138.1 (2C; C-5), 133.6 (2C; C-10), 126.4 (2CH; C-1), 114.8 (2CH; C-4), 112.2 (2CH; C-2), 87.5 (2C; C≡C), 79.8 (2C; C-17), 74.8 (2C; C≡C), 74.1 (2CH; C≡CH), 70.9 (2C; C≡C), 56.1 ($2OCH_2$), 49.4 (2CH; C-14), 47.1 (2C; C-13), 43.5 (2CH; C-9), 39.2 (2CH; C-8), 38.9 ($2CH_2$; C-16), 32.7 ($2CH_2$; C-12), 29.7 ($2CH_2$; C-6), 27.1 ($2CH_2$; C-7), 26.3 ($2CH_2$; C-11), 22.8 ($2CH_2$; C-15), 12.6 ppm ($2CH_3$; C-18); IR (KBr): $\tilde{\nu}$=3417, 3287, 2932, 2869, 1605, 1498, 1229, 1026, 753 cm^{-1}; MS (APCI): *m/z*: 667 $[M+H]^+$, 649 $[M-H_2O+H]^+$, 631 $[M-2H_2O+H]^+$; elemental analysis calcd (%) for $C_{46}H_{50}O_4$: C 82.85, H 7.56; found: C 83.11, H 7.40.

Macrocycles 41 and 44: A mixture of pyridine (8 mL) and CH_3CN (25 mL) was heated at reflux for 1 h. Dimer **43** (50 mg, 0.075 mmol, 1.0 equiv) and $Cu(OAc)_2{\cdot}H_2O$ (75 mg, 0.375 mmol, 5.0 equiv) were then successively added, and the mixture was refluxed for a further 1 h. It was then allowed to cool to room temperature, quenched with ice, diluted with CH_2Cl_2 (40 mL), and washed with H_2O (4×50 mL). The organic layer was dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuo. Chromatography on silica gel (hexanes/AcOEt 4:1) of the residue afforded 31 mg (66%) of the desired pure macrocycle **41** together with

9 mg (18%) of pure **44**, both as white solids. **41**: M.p. 260°C (decomp.); $[\alpha]_D^{20}=-64.43$ ($c=0.39$ in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta=7.25$ (d, $J=8.6$ Hz, 4H; H-1), 6.70 (dd, $J=8.6$, 2.8 Hz, 4H; H-2), 6.65 (d, $J=2.8$ Hz, 4H; H-4), 4.75 (d, $J=7.0$ Hz, 4H; OCH_2), 4.72 (d, $J=7.0$ Hz, 4H; OCH_2), 2.81 (m, 8H), 2.39–2.30 (m, 8H), 2.18–1.92 (m, 12H), 1.90–1.64 (m, 16H), 1.62–1.22 (m, 20H), 0.92 ppm (s, 12H; H-18); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta=154.3$ (4C; C-3), 138.1 (4C; C-5), 132.4 (4C; C-10), 126.9 (4CH; C-1), 116.7 (4CH; C-4), 110.4 (4CH; C-2), 83.0 (4C; C≡C), 80.4 (4C; C-17), 74.5 (4C; C≡C), 71.1 (4C; C≡C), 69.8 (4C; C≡C), 55.0 ($4OCH_2$), 50.4 (4CH; C-14), 48.2 (4C; C-13), 44.7 (4CH; C-9), 39.1 (4CH; C-8), 38.6 ($4CH_2$; C-16), 33.4 ($4CH_2$; C-12), 29.9 ($4CH_2$; C-6), 27.1 ($4CH_2$; C-7), 26.1 ($4CH_2$; C-11), 22.7 ($4CH_2$; C-15), 13.0 ppm ($4CH_3$; C-18); IR (KBr): $\tilde{\nu}=3447$, 2930, 2867, 1609, 1498, 1260, 1024 cm^{-1}; MS (ESI): m/z: 1294.8 $[M-2H_2O+H]^+$; elemental analysis calcd (%) for $C_{92}H_{96}O_8$: C 83.10, H 7.28; found: C 83.41, H 7.51. **44**: M.p. 310°C (decomp.); $[\alpha]_D^{20}=-36.19$ ($c=0.84$ in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta=7.20$ (d, $J=8.5$ Hz, 8H; H-1), 6.76 (dd, $J=8.5$, 2.4 Hz, 8H; H-2), 6.64 (d, $J=2.4$ Hz, 8H; H-4), 4.72 (s, 16H; OCH_2), 2.84 (m, 16H), 2.39–2.20 (m, 16H), 2.03 (brt, $J=11.9$ Hz, 8H), 1.90–1.60 (m, 40H), 1.50–1.20 (m, 48H), 0.88 ppm (s, 24H; H-18); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta=155.0$ (8C; C-3), 138.1 (8C; C-5), 133.5 (8C; C-10), 126.3 (8CH; C-1), 115.4 (8CH; C-4), 111.8 (8CH; C-2), 83.4 (8C; C≡C), 80.7 (8C; C-17), 74.9 (8C; C≡C), 71.1 (8C; C≡C), 70.4 (8C; C≡C), 55.8 ($8OCH_2$), 49.8 (8CH; C-14), 47.9 (8C; C-13), 43.4 (8CH; C-9), 39.3 (8CH; C-8), 38.8 ($8CH_2$; C-16), 33.0 ($8CH_2$; C-12), 29.7 ($8CH_2$; C-6), 27.2 ($8CH_2$; C-7), 26.3 ($8CH_2$; C-11), 22.9 ($8CH_2$; C-15), 12.8 ppm ($8CH_3$; C-18); IR (KBr): $\tilde{\nu}=3436$, 2927, 2856, 1610, 1497, 1453, 1228, 1028, 874 cm^{-1}; MS (ESI): m/z: 2682.5 $[M+Na]^+$; elemental analysis calcd (%) for $C_{184}H_{192}O_{16}$: C 83.10, H 7.28; found: C 82.88, H 7.02.

Compound 45b: A mixture of triazide **34b** (145.5 mg, 0.444 mmol, 1.0 equiv), bis(alkyne) **38** (541.6 mg, 1.322 mmol, 3.0 equiv), sodium L-ascorbate (26.3 mg, 0.133 mmol, 0.6 equiv), and $CuSO_4\cdot5H_2O$ (16.7 mg, 0.067 mmol, 0.3 equiv) in DMF (20 mL) was stirred under Ar at RT for 1.5 h. The reaction was then quenched with water, the resulting mixture was extracted with AcOEt (150 mL), and the organic extract was washed with water (2×150 mL) and brine (1×150 mL). The organic layer was dried over $MgSO_4$, filtered, and the solvent was removed in vacuo. The resulting white solid was purified by passage through a short pad of SiO_2 (hexane/AcOEt 2:1 to 1:1) to yield **45b** as a white solid (516.4 mg, 75%). M.p. 155–156°C; $[\alpha]_D^{25}=-10.21$ ($c=0.48$ in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta=7.37$ (s, 3H; N_3C=CH), 7.20 (d, $J=8.7$ Hz, 3H; H-1), 6.75 (dd, $J=8.7$, 2.4 Hz, 3H; H-2), 6.68 (d, $J=2.4$ Hz, 3H; H-4), 5.64 (s, 6H), 5.13 (s, 6H), 2.80 (m, 12H), 2.36–2.26 (m, 6H), 2.17 (m, 3H), 2.04–1.62 (m, 21H), 1.50–1.26 (m, 12H), 0.94 (t, $J=7.2$ Hz, 9H; CH_2CH_3), 0.86 (s, 9H; H-18), 0.17 ppm (s, 27H; TMS); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta=$ 156.0 (3C; C-3), 146.5 (3C; Ar), 144.7 (3C; N_3C=CH), 138.1 (3C; C-5), 133.2 (3C; C-10), 129.6 (3C; Ar), 126.4 (3CH; C-1), 122.0 (3CH; N_3C=CH), 114.8 (3CH; C-4), 112.3 (3CH; C-2), 109.4 (3C_{sp}; C≡C), 90.1 (3C_{sp}; C≡C), 80.1 (3C; C-17), 62.0 ($3CH_2$), 49.6 (3CH; C-14), 47.9 ($3CH_2$), 47.2 (3C; C-13), 43.7 (3CH; C-9), 39.4 (3CH; C-8), 38.9 ($3CH_2$; C-16), 32.8 ($3CH_2$; C-12), 29.8 ($3CH_2$; C-6), 27.2 ($3CH_2$; C-7), 26.4 ($3CH_2$; C-11), 23.6 ($3CH_2$), 22.8 ($3CH_2$; C-15), 15.2 ($3CH_3$), 12.8 ($3CH_3$; C-18), 0.03 ppm ($9CH_3$; TMS); IR (KBr): $\tilde{\nu}=3436$, 2933, 2872, 2159, 1609, 1498, 1455, 1381, 1250, 1046, 843 cm^{-1}; MS (ES): m/z: 1548.2 $[M+H]^+$.

Compound 46a: A solution of nBu$_4$NF·3H$_2$O (118.6 mg, 0.376 mmol) in THF (3 mL) was added dropwise to a solution of TMS-protected trialkyne **45a** (166.3 mg, 0.114 mmol) in THF (9 mL) at 0°C. The resulting mixture was stirred for 30 min at the same temperature. The solvent was then removed in vacuo and the concentrated mixture was filtered through a short pad of silica gel (10×2 cm, hexanes/AcOEt 1:2 to 1:4) to yield terminal trialkyne **46a** as a white solid (139.2 mg, 98%). M.p. 165–167°C; $[\alpha]_D^{29}=+2.50$ ($c=0.60$ in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta=7.56$ (s, 3H; N_3C=CH), 7.19 (d, $J=8.7$ Hz, 3H; H-1), 7.13 (s, 3H; Ar), 6.75 (dd, $J=8.7$, 2.7 Hz, 3H; H-2), 6.69 (d, $J=2.7$ Hz, 3H; H-4), 5.47 (s, 6H), 5.15 (s, 6H), 2.81 (m, 6H), 2.60 (s, 3H; C≡CH), 2.36–2.17 (m, 9H), 2.06–1.65 (m, 21H), 1.53–1.26 (m, 12H), 0.87 ppm (s, 9H; H-18); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta=156.0$ (3C; C-3), 145.3 (3C; N_3C=CH), 138.1 (3C; C-5), 136.8 (3C; Ar), 133.3 (3C; C-10), 127.5 (3CH; Ar), 126.4 (3CH; C-1), 122.8 (3CH; N_3C=CH), 114.7 (3CH; C-4), 112.1 (3CH; C-2), 87.5 (3C_{sp}; C≡C), 79.8 (3C; C-17), 74.0 (3C_{sp}; C≡CH), 62.0 ($3CH_2$), 53.3 ($3CH_2$), 49.4 (3CH; C-14), 47.1 (3C; C-13), 43.5 (3CH; C-9), 39.3 (3CH; C-8), 38.9 ($3CH_2$; C-16), 32.7 ($3CH_2$; C-12), 29.8 ($3CH_2$; C-6), 27.2 ($3CH_2$; C-7), 26.3 ($3CH_2$; C-11), 22.8 ($3CH_2$; C-15), 12.7 ppm ($3CH_3$; C-18); IR (KBr): $\tilde{\nu}=3435$, 3299, 2931, 2870, 1609, 1576, 1497, 1252, 1233, 1051, 1016 cm^{-1}; MS (ES): m/z: 1247.2 $[M+H]^+$; elemental analysis calcd (%) for $C_{78}H_{87}N_9O_6$: C 75.15, H 7.03, N 10.11; found: C 74.90, H 6.88, N 10.33.

Compound 46b: A solution of nBu$_4$NF·3H$_2$O (335.1 mg, 1.062 mmol) in THF (5 mL) was added dropwise to a solution of TMS-protected trialkyne **45b** (457.2 mg, 0.295 mmol) in THF (15 mL) at 0°C. The resulting mixture was stirred for 30 min at the same temperature. The solvent was then removed in vacuo and the concentrated mixture was filtered through a short pad of silica gel (10×2 cm, AcOEt) to yield terminal trialkyne **46b** as a white solid (355.6 mg, 91%). M.p. 148–150°C; $[\alpha]_D^{25}=-3.53$ ($c=0.17$ in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta=7.36$ (s, 3H; N_3C=CH), 7.16 (d, $J=8.4$ Hz, 3H; H-1), 6.73 (dd, $J=8.4$, 2.4 Hz, 3H; H-2), 6.67 (d, $J=2.4$ Hz, 3H; H-4), 5.64 (s, 6H), 5.12 (s, 6H), 2.79 (m, 12H), 2.61 (s, 3H; C≡CH), 2.38–2.29 (m, 6H), 2.24–2.17 (brt, $J=12.0$ Hz, 3H; CH_2CH_3), 2.07–1.30 (m, 33H), 0.95 (t, $J=7.2$ Hz, 9H; CH_2CH_3), 0.88 ppm (s, 9H; H-18); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta=156.0$ (3C; C-3), 146.5 (3C; Ar), 144.7 (3C; N_3C=CH), 138.0 (3C; C-5), 133.2 (3C; C-10), 129.6 (3C; Ar), 126.4 (3CH; C-1), 122.0 (3CH; N_3C=CH), 114.7 (3CH; C-4), 112.2 (3CH; C-2), 87.5 (3C_{sp}; C≡C), 79.8 (3C; C-17), 74.0 (3C_{sp}; C≡CH), 62.0 ($3CH_2$), 49.4 (3CH; C-14), 47.9 ($3CH_2$), 47.1 (3C; C-13), 43.5 (3CH; C-9), 39.3 (3CH; C-8), 38.9 ($3CH_2$; C-16), 32.7 ($3CH_2$; C-12), 29.7 ($3CH_2$; C-6), 27.2 ($3CH_2$; C-7), 26.3 ($3CH_2$; C-11), 23.6 ($3CH_2$), 22.8 ($3CH_2$; C-15), 15.3 ($3CH_3$), 12.7 ppm ($3CH_3$; C-18); IR (KBr): $\tilde{\nu}=$ 3436, 2931, 2871, 1609, 1497, 1454, 1380, 1280, 1232, 1145, 1047 cm^{-1}; MS (ES): m/z: 1330.9 $[M+H]^+$, 1352.9 $[M+Na]^+$; elemental analysis calcd (%) for $C_{84}H_{99}N_9O_6$: C 75.81, H 7.50, N 9.47; found: C 75.55, H 7.38, N 9.60.

Compound 46c: A solution of nBu$_4$NF·3H$_2$O (188.7 mg, 0.598 mmol) in THF (4 mL) was added dropwise to a solution of TMS-protected trialkyne **45c** (234.8 mg, 0.166 mmol) in THF (6 mL) at 0°C. The resulting mixture was stirred for 30 min at the same temperature. The solvent was then removed in vacuo and the concentrated mixture was filtered through a short pad of silica gel (10×2 cm, AcOEt/hexane 1:2 to 1:5) to yield terminal trialkyne **46c** as a white solid (175.4 mg, 88%). M.p. 123–125°C; $[\alpha]_D^{25}=+2.16$ ($c=0.37$ in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta=8.03$ (s, 3H; N_3C=CH), 7.21 (d, $J=8.7$ Hz, 3H; H-1), 6.79 (dd, $J=8.7$, 2.4 Hz, 3H; H-2), 6.72 (d, $J=2.4$ Hz, 3H; H-4), 5.20 (s, 6H), 4.41 (s, 6H), 2.83 (m, 6H), 2.60 (s, 3H; C≡CH), 2.38–2.30 (m, 6H), 2.25–2.17 (m, 3H), 2.07–1.65 (m, 21H), 1.55–1.32 (m, 12H), 0.88 (s, 9H; H-18), 0.84 ppm (s, 3H; CH_3); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta=156.0$ (3C; C-3), 144.5 (3C; N_3C=CH), 138.1 (3C; C-5), 133.4 (3C; C-10), 126.4 (3CH; C-1), 125.6 (3CH; N_3C=CH), 114.9 (3CH; C-4), 112.3 (3CH; C-2), 87.5 (3C_{sp}; C≡C), 79.8 (3C; C-17), 74.0 (3C_{sp}; C≡CH), 61.9 ($3CH_2$), 53.4 ($3CH_2$), 49.4 (3CH; C-14), 47.1 (3C; C-13), 43.5 (3CH; C-9), 41.6 (C), 39.3 (3CH; C-8), 39.0 ($3CH_2$; C-16), 32.7 ($3CH_2$; C-12), 29.8 ($3CH_2$; C-6), 27.2 ($3CH_2$; C-7), 26.4 ($3CH_2$; C-11), 22.8 ($3CH_2$; C-15), 19.2 (CH_3), 12.7 ppm ($3CH_3$; C-18); IR (KBr): $\tilde{\nu}=3435$, 3298, 3145, 2932, 2870, 1608, 1497, 1455, 1234, 1049, 755 cm^{-1}; MS (ES): m/z: 1199.2 $[M+H]^+$; elemental analysis calcd (%) for $C_{74}H_{87}N_9O_6$: C 74.16, H 7.32, N 10.52; found: C 74.30, H 7.15, N 10.37.

Compound 47: A mixture of triazide **34c** (15.0 mg, 0.077 mmol, 1.0 equiv), alkyne **46b** (102.0 mg, 0.077 mmol, 1.0 equiv), sodium L-ascorbate (30.5 mg, 0.154 mmol, 2.0 equiv), and $CuSO_4\cdot5H_2O$ (19.2 mg, 0.077 mmol, 1.0 equiv) in DMF (150 mL) was stirred under Ar at RT for 3 days. The reaction was then quenched with water, the resulting mixture was extracted with AcOEt (150 mL), and the organic extract was washed with water (2×150 mL) and brine (1×150 mL). The organic layer was dried over $MgSO_4$, filtered, and the solvent was removed in vacuo. The resulting white solid was purified by column chromatography (15×1.5 cm, SiO_2; AcOEt to AcOEt/MeOH 5:1) to yield **47** as a white solid (29.4 mg, 25%). M.p. 245°C (decomp.); $[\alpha]_D^{28}=+14.44$ ($c=0.27$ in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$/CD_3OD): $\delta=7.99$ (brs), 7.83 (brs), 7.69 (brs), 7.60 (brs), 7.40 (brs), 7.30–7.22 (m), 6.89 (d, $J=9.2$ Hz), 6.78

(m), 6.70 (d, $J=8.8$ Hz), 6.51–6.40 (m), 5.62–5.54 (m), 4.91–4.83 (m), 4.63 (d, $J=14.4$ Hz), 4.54 (d, $J=14.4$ Hz), 4.33 (m), 4.22 (m), 4.10–4.07 (m), 3.91 (br s), 2.57 (m), 2.32 (m), 2.19 (m), 2.04 (m), 1.82–1.67 (m), 1.56–1.44 (m), 1.35–1.04 (m), 0.92 (s), 0.88 (s), 0.76 (m), 0.51–0.35 ppm (m); ^{13}C NMR (75 MHz, $CDCl_3/CD_3OD$): $\delta=156.0$, 155.9, 155.9, 155.8, 155.7 (C; C-3), 153.9, 153.5, 153.4, 152.9 (C; N_3C=CH), 146.8, 146.7, 146.6 (C; Ar), 144.5, 144.3, 144.2, 144.1 (C; N_3C=CH), 138.0, 137.9, 137.7, 137.6 (C; C-5), 133.1, 133.0, 132.8 (C; C-10), 129.5, 129.4, 129.3, 129.2 (C; Ar), 126.0, 125.7 (CH; C-1), 124.9, 124.8 (×2), 124.6 (×2), 124.5 (CH; N_3C=CH), 121.8, 121.7, 121.1 (CH; N_3C=CH), 114.7, 114.2, 113.9 (CH; C-4), 113.0, 112.3 (CH; C-2), 82.1, 81.9, 81.7, 81.6 (C; C-17), 62.1, 61.8, 61.7 (CH_2), 53.5 (CH_2), 48.5 (×2) (CH; C-14), 47.6 (CH_2), 47.4, 47.2, 47.1 (C; C-13), 43.4, 43.3, 43.1 (CH; C-9), 42.2, 41.6 (CH_3C), 39.3, 39.0 (CH; C-8), 37.7, 37.4 (CH_2; C-16), 33.0 (×2), 32.9 (×2) (CH_2; C-12), 29.6, 29.5, 29.0 (CH_2; C-6), 27.5, 27.2 (CH_2; C-7), 25.9, 25.8, 25.7 (CH_2; C-11), 23.4, 23.2, 23.1, 23.0 (CH_2; C-15 + CH_2Ar), 19.4, 19.2 (CH_3C), 15.7, 15.6, 15.5 (CH_3Ar), 14.3, 14.1, 14.0 ppm (CH_3; C-18); IR (KBr): $\tilde{\nu}=3436$, 2930, 2872, 1609, 1497, 1455, 1380, 1281, 1232, 1047, 754 cm^{-1}; MS (ES): *m/z*: 1527.3 $[M+H]^+$; elemental analysis calcd (%) for $C_{89}H_{108}N_{18}O_6$: C 70.05, H 7.13, N 16.52; found: C 69.80, H 6.84, N 16.21.

Tripod 48: NaH (458 mg, 11.44 mmol, 60% in mineral oil) was added in one portion to a solution of estrone (**49**) (1.00 g, 3.70 mmol) in dry DMF (100 mL) at 0°C under argon. After stirring for 10 min, the mixture was allowed to warm to RT and then stirred for a further 10 min. It was then cooled to 0°C once more, whereupon 1,3,5-tris(bromomethyl)-2,4,6-triethylbenzene[42] (542 mg, 1.23 mmol) was added in one portion. The mixture was allowed to warm to room temperature and was then heated at 70°C for 12 h. Thereafter, the reaction was quenched with H_2O at 0°C. After neutralizing the diluted mixture with 0.1 M HCl, it was extracted with CH_2Cl_2 (3×100 mL). The combined organic layers were washed twice with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuo. Filtration of the crude residue through a short pad of silica gel (CH_2Cl_2/MeOH 100:1 to 25:1) yielded 956 mg (77%) of pure **48** as a white solid. M.p. 178–180°C; $[\alpha]_D^{24}=+123.74$ ($c=0.91$ in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta=7.30$ (d, $J=8.7$ Hz, 3H; H-1), 6.90 (dd, $J=8.7$, 2.4 Hz, 3H; H-2), 6.83 (d, $J=2.4$ Hz, 3H; H-4), 5.09 (s, 6H; OCH_2), 2.98 (m, 6H), 2.86 (m, 6H), 2.59–2.44 (m, 6H), 2.32–1.99 (m, 15H), 1.71–1.47 (m, 18H), 1.28 (t, $J=7.2$ Hz, 9H; CH_3), 0.95 ppm (s, 9H; H-18); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta=220.8$ (3C=O; C-17), 156.8 (3C; C-3), 146.0 (3C), 137.8 (3C; C-5), 132.2 (3C; C-10), 131.0 (3C), 126.4 (3CH; C-1), 114.3 (3CH; C-4), 112.1 (3CH; C-2), 63.8 ($3OCH_2$), 50.3 (3CH; C-14), 47.9 (3C; C-13), 43.9 (3CH; C-9), 38.3 (3CH; C-8), 35.8 ($3CH_2$; C-16), 31.5 ($3CH_2$; C-12), 29.6 ($3CH_2$; C-6), 26.5 ($3CH_2$; C-7), 25.8 ($3CH_2$; C-11), 22.9 ($3CH_2$; ArCH_2), 21.5 ($3CH_2$; C-15), 16.5 ($3CH_3$), 13.8 ppm ($3CH_3$; C-18); IR (KBr): $\tilde{\nu}=3436$, 2930, 1740, 1607, 1574, 1496, 1454, 1373, 1279, 1229, 1006 cm^{-1}; MS (ESI): *m/z*: 1010.0 $[M+H]^+$; elemental analysis calcd (%) for $C_{69}H_{84}O_6$: C 82.10, H 8.39; found: C 82.45, H 8.17.

Compound 50: LiHMDS (4.46 mmol, 4.5 mL, 1.0 M in THF) was added dropwise to a solution of ethynyltrimethylsilane (438 mg, 4.46 mmol) in THF (100 mL) at −78°C. The mixture was stirred at the same temperature for 30 min and then warmed to 0°C, whereupon a solution of tripod **48** (0.50 g, 0.495 mmol) in THF (20 mL) was added dropwise via a cannula. The reaction mixture was allowed to reach room temperature, stirred overnight, and subsequently quenched at 0°C with saturated aqueous NH_4Cl solution. The resulting mixture was extracted with AcOEt (3×25 mL), and the combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuo. Chromatography on silica gel (25×3 cm, hexanes/AcOEt 10:1 to 4:1) of the crude residue yielded 342 mg (53%) of pure **50** as a white solid. M.p. 158–160°C; $[\alpha]_D^{25}=-10.36$ ($c=0.28$ in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta=7.34$ (d, $J=8.7$ Hz, 3H; H-1), 6.92 (br d, $J=8.7$ Hz, 3H; H-2), 6.84 (br s, 3H; H-4), 5.11 (s, 6H; OCH_2), 2.91 (m, 12H), 2.47–2.33 (m, 9H), 2.16–1.71 (m, 21H), 1.63–1.45 (m, 12H), 1.30 (t, $J=6.9$ Hz, 9H; CH_3), 0.94 (s, 9H; H-18), 0.25 ppm (s, 27H; TMS); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta=156.7$ (3C; C-3), 146.0 (3C), 138.0 (3C; C-5), 132.7 (3C; C-10), 131.1 (3C), 126.4 (3CH; C-1), 114.2 (3CH; C-4), 112.1 (3CH; C-2), 109.5 ($3C_{sp}$; C≡C), 89.9 ($3C_{sp}$; C≡C), 80.0 (3C; C-17), 63.8 ($3OCH_2$), 49.5 (3CH; C-14), 47.2 (3C; C-13), 43.7 (3CH; C-9), 39.4 (3CH; C-8), 38.9 ($3CH_2$; C-16), 32.8 ($3CH_2$; C-12), 29.9 ($3CH_2$; C-6), 27.3 ($3CH_2$; C-7), 26.4 ($3CH_2$; C-11), 22.8 ($6CH_2$; C-15 + ArCH_2), 16.5 ($3CH_3$), 12.8 ($3CH_3$; C-18), 0.02 ppm ($9CH_3$; TMS); IR (KBr): $\tilde{\nu}=3437$, 2951, 2932, 2872, 2160, 1608, 1575, 1496, 1249, 1017, 843 cm^{-1}; MS (ESI): *m/z*: 1287.2 $[M+H-H_2O]^+$.

Desilylation of compound 50—preparation of compound 51: A solution of nBu$_4$NF·3H$_2$O (202 mg, 0.640 mmol) in THF (3 mL) was added dropwise to a solution of TMS-protected tripod **50** (253 mg, 0.194 mmol) in THF (7 mL) at 0°C. The resulting mixture was stirred for 30 min at this temperature. The solvent was then removed in vacuo and the concentrated mixture was filtered through a short pad of silica gel (10×2 cm, hexanes/AcOEt 1:1 to 1:2) to yield 207 mg (98%) of pure tripod **51** as a white solid. M.p. 173–175°C; $[\alpha]_D^{26}=+5.00$ ($c=0.12$ in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta=7.30$ (d, $J=8.7$ Hz, 3H; H-1), 6.89 (br d, $J=8.7$ Hz, 3H; H-2), 6.81 (br s, 3H; H-4), 5.08 (s, 6H; OCH_2), 2.92–2.85 (m, 12H), 2.64 (s, 3H), 2.44–2.26 (m, 9H), 2.01–1.71 (m, 21H), 1.61–1.39 (m, 12H), 1.27 (t, $J=7.2$ Hz, 9H; CH_3), 0.92 ppm (s, 9H; H-18); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta=156.8$ (3C; C-3), 146.0 (3C), 138.0 (3C; C-5), 132.8 (3C; C-10), 131.1 (3C), 126.4 (3CH; C-1), 114.2 (3CH; C-4), 112.1 (3CH; C-2), 87.5 ($3C_{sp}$; C≡C), 79.8 (3C; C-17), 74.0 ($3C_{sp}$; C≡C), 63.9 ($3OCH_2$), 49.4 (3CH; C-14), 47.1 (3C; C-13), 43.5 (3CH; C-9), 39.4 (3CH; C-8), 38.9 ($3CH_2$; C-16), 32.7 ($3CH_2$; C-12), 29.9 ($3CH_2$; C-6), 27.2 ($3CH_2$; C-7), 26.4 ($3CH_2$; C-11), 22.9 ($3CH_2$; ArCH_2), 22.8 ($3CH_2$; C-15), 16.5 ($3CH_3$), 12.7 ppm ($3CH_3$; C-18); IR (KBr): $\tilde{\nu}=3437$, 3303, 2932, 2871, 1607, 1574, 1495, 1229, 1145, 1047, 1014 cm^{-1}; MS (ESI): *m/z*: 1069.9 $[M+H-H_2O]^+$, 1087.2 $[M+H]^+$; elemental analysis calcd (%) for $C_{75}H_{90}O_6$: C 82.83, H 8.34; found: C 82.69, H 8.57.

Compound 52: A solution of tripod **51** (50.0 mg, 0.046 mmol) in dry pyridine (14 mL)/CH_3CN (42 mL) was heated at reflux for 30 min under argon. Cu(OAc)$_2$·H$_2$O (68.9 mg, 0.345 mmol) was added and the mixture was refluxed for a further 1 h. The reaction mixture was then allowed to cool to RT, quenched with ice, diluted with AcOEt, and washed three times with H_2O. The organic layer was dried over anhydrous Na_2SO_4 and the solvents were removed in vacuo. Column chromatography (hexanes/AcOEt 10:1 to 1:1) of the resulting residue yielded 20.4 mg (41%) of pure estrone-based cage **52** as a white solid. M.p. 300°C (decomp.); $[\alpha]_D^{28}=+3.27$ ($c=0.55$ in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3/CD_3OD$): $\delta=7.04$ (d, $J=8.7$ Hz, 6H), 6.76 (br d, $J=8.7$ Hz, 6H), 6.72 (br s, 6H), 5.04 (d, $J=9.9$ Hz, 6H), 4.89 (d, $J=9.9$ Hz, 6H), 2.84–2.77 (m, 24H), 2.39 (s, 6H; OH), 2.23–2.15 (m, 18H), 1.93–1.66 (m, 36H), 1.48–1.30 (m, 24H), 1.18 (t, $J=7.5$ Hz, 18H), 0.84 ppm (s, 18H; H-18); ^{13}C NMR (75 MHz, $CDCl_3/CD_3OD$): $\delta=156.7$ (6C; C-3), 145.9 (6C), 137.4 (6C; C-5), 131.6 (6C; C-10), 130.8 (6C), 127.0 (6CH; C-1), 113.9 (6CH; C-4), 112.4 (6CH; C-2), 85.5 ($6C_{sp}$; C≡C), 79.7 (6C; C-17), 69.7 ($6C_{sp}$; C≡C), 63.5 ($6OCH_2$), 49.8 (6CH; C-14), 48.9 (6C; C-13), 44.7 (6CH; C-9), 39.4 (6CH; C-8), 37.8 ($6CH_2$; C-16), 33.0 ($6CH_2$; C-12), 30.1 ($6CH_2$; C-6), 27.1 ($6CH_2$; C-7), 26.8 ($6CH_2$; C-11), 22.7 ($12CH_2$; C-15 + ArCH_2), 16.5 ($6CH_3$), 12.7 ppm ($6CH_3$; C-18); IR (KBr): $\tilde{\nu}=3437$, 2930, 2871, 1608, 1575, 1496, 1454, 1279, 1229, 1138, 1047, 1011 cm^{-1}; MS (MALDI): *m/z*: 2191.3 $[M+Na]^+$, 2207.3 $[M+K]^+$; elemental analysis calcd (%) for $C_{150}H_{174}O_{12}$: C 83.06, H 8.09; found: C 83.38, H 7.75.

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[1] a) R. Breinbauer, I. R. Vetter, H. Waldmann, *Angew. Chem.* **2002**, *114*, 3002; *Angew. Chem. Int. Ed.* **2002**, *41*, 2878; b) I. Paterson, E. A. Anderson, *Science* **2005**, *310*, 451; c) D. J. Newman, G. M.

Cragg, *J. Nat. Prod.* **2007**, *70*, 461; d) F. E. Koehn, G. T. Carter, *Nat. Rev. Drug. Discovery* **2005**, *4*, 206.

[2] Natural product hybrids are a combination of parts of natural product fragments. See: a) L. F. Tietze, H. P. Bell, S. Chandrasekhar, *Angew. Chem.* **2003**, *115*, 4128; *Angew. Chem. Int. Ed.* **2003**, *42*, 3996; b) G. Mehta, V. Singh, *Chem. Soc. Rev.* **2002**, *31*, 324.

[3] Diversity-oriented synthesis concept (DOS): a) S. L. Schreiber, *Science* **2000**, *287*, 1964; b) S. L. Schreiber, *Chem. Eng. News* **2003**, *81*, 51; c) M. D. Burke, S. L. Schreiber, *Angew. Chem.* **2004**, *116*, 48; *Angew. Chem. Int. Ed.* **2004**, *43*, 46. For recent reviews on DOS, see: d) R. J. Spandl, A. Bender, D. R. Spring, *Org. Biomol. Chem.* **2008**, *6*, 1149; e) R. J. Spandl, M. Díaz-Gavilán, K. M. G. O'Connell, G. L. Thomas, D. R. Spring, *Chem. Rec.* **2008**, *8*, 129; f) C. Cordier, D. Morton, S. Murrison, A. Nelson, C. O'Leary-Steele, *Nat. Prod. Rep.* **2008**, *25*, 719; g) T. E. Nielsen, S. L. Schreiber, *Angew. Chem.* **2008**, *120*, 52; *Angew. Chem. Int. Ed.* **2008**, *47*, 48; h) D. S. Tan, *Nat. Chem. Biol.* **2005**, *1*, 74.

[4] a) S. T. Diver, S. L. Schreiber, *J. Am. Chem. Soc.* **1997**, *119*, 5106; b) F. Grellepois, B. Crousse, D. Bonnet-Delpon, J. P. Bégué, *Org. Lett.* **2005**, *7*, 5219; c) J. P. Sestelo, A. Mouriño, L. A. Sarandeses, *Org. Lett.* **1999**, *1*, 1005; d) A. Fürstner, T. Gastner, H. Weintritt, *J. Org. Chem.* **1999**, *64*, 2361; e) P. E. Harrington, M. A. Tius, *Org. Lett.* **1999**, *1*, 649; f) A. B. Smith III, C. M. Adams, S. A. Kozmin, D. V. Paone, *J. Am. Chem. Soc.* **2001**, *123*, 5925.

[5] G. C. Tron, T. Pirali, R. A. Billington, P. L. Canonico, G. Sorba, A. A. Genazzani, *Med. Res. Rev.* **2008**, *28*, 278.

[6] M. C. de La Torre, A. M. Deometrio, E. Álvaro, I. García, M. A. Sierra, *Org. Lett.* **2006**, *8*, 593.

[7] M. A. Sierra, R. M. Torres, M. C. de la Torre, E. Álvaro, *J. Org. Chem.* **2007**, *72*, 4213.

[8] E. Álvaro, M. C. de la Torre, M. A. Sierra, *Chem. Eur. J.* **2006**, *12*, 6403.

[9] E. Álvaro, M. C. de la Torre, M. A. Sierra, *Chem. Commun.* **2006**, 985.

[10] P. Ramírez-López, M. C. de la Torre, H. Montenegro, M. Asenjo, M. A. Sierra, *Org. Lett.* **2008**, *10*, 3555.

[11] a) C. Glaser, *Ber. Dtsch. Chem. Ges.* **1869**, *2*, 422; b) A. S. Hay, *J. Org. Chem.* **1962**, *27*, 3320; c) G. Eglinton, A. R. Galbraith, *Chem. Ind.* **1956**, 737; for an overview of acetylenic homo-coupling, see: d) P. Siemsen, R. C. Livingston, F. Diederich, *Angew. Chem.* **2000**, *112*, 2740; *Angew. Chem. Int. Ed.* **2000**, *39*, 2632, and references therein. For a review on copper-mediated couplings, see: e) G. Evano, N. Blanchard, M. Toumi, *Chem. Rev.* **2008**, *108*, 3054.

[12] a) C. W. Tornøe, C. Christensen, M. Meldal, *J. Org. Chem.* **2002**, *67*, 3057; b) V. V. Rostovtsev, L. G. Green, V. V. Fokin, K. B. Sharpless, *Angew. Chem.* **2002**, *114*, 2708; *Angew. Chem. Int. Ed.* **2002**, *41*, 2596; for selected reviews on the copper(I)-catalyzed azide–alkyne reaction, see: c) M. Meldal, C. W. Tornøe, *Chem. Rev.* **2008**, *108*, 2952; d) V. D. Bock, H. Hiemstra, J. H. van Maarseveen, *Eur. J. Org. Chem.* **2006**, 51; e) W. H. Binder, R. Sachsenhofer, *Macromol. Rapid Commun.* **2007**, *28*, 15; f) H. Nandivada, X. Jiang, J. Lahann, *Adv. Mater.* **2007**, *19*, 2197.

[13] P. Crabbe, J. A. Zderic, *Bull. Soc. Chim. Belg.* **1961**, *70*, 403.

[14] Selected examples in oligo- and polysaccharide chemistry: a) S. Muthana, H. Yu, S. Huang, X. Chen, *J. Am. Chem. Soc.* **2007**, *129*, 11918; b) A. Dondoni, A. Marra, *J. Org. Chem.* **2006**, *71*, 7546; c) E. Fernández-Megia, J. Correa, R. Riguera, *Biomacromolecules* **2006**, *7*, 3104; d) K. D. Bodine, D. Y. Gin, M. S. Gin, *J. Am. Chem. Soc.* **2004**, *126*, 1638; for a review on the Huisgen Cu^{I}-catalyzed azide–alkyne 1,3-dipolar cycloaddition reaction in nucleoside, nucleotide, and oligonucleotide chemistry, see: e) F. Amblard, J. H. Cho, R. F. Schinazi, *Chem. Rev.* **2009**, *109*, 4207.

[15] Selected examples concerning glycopeptides: a) Q. Wan, J. Chen, G. Chen, S. J. Danishefsky, *J. Org. Chem.* **2006**, *71*, 8244; b) H. Lin, C. T. Walsh, *J. Am. Chem. Soc.* **2004**, *126*, 13998; c) C. Palomo, J. M. Aizpurua, E. Balentová, I. Azcune, J. I. Santos, J. Jiménez-Barbero, J. Cañada, J. I. Miranda, *Org. Lett.* **2008**, *10*, 2227.

[16] V. O. Rodionov, S. I. Presolski, S. Gardinier, Y.-H. Lim, M. G. Finn, *J. Am. Chem. Soc.* **2007**, *129*, 12696.

[17] These compounds facilitate the dissolution of the hydrophilic dye cresol red in nonpolar organic solvents; see: N. G. Aher, V. S. Pore, S. P. Patil, *Tetrahedron* **2007**, *63*, 12927.

[18] Comparison of the ^{13}C NMR signals of the terpenic domain of **12** with those of a related camphor derivative, the structure of which was determined by X-ray diffraction analysis, allowed us to establish the stereochemistry at the carbinol center; see: M. Czugler, P. P. Korkas, P. Bombicz, W. Seichter, E. Weber, *Chirality* **1997**, *9*, 203.

[19] The stereochemistry at the formed tertiary carbinol center of alkyne **13** was established by comparison of the ^{13}C NMR data of the terpenic domain with those of related derivatives, see: L. Zhao, D. J. Burnell, *Tetrahedron Lett.* **2006**, *47*, 3291.

[20] Comparison of the ^{13}C NMR signals of the steroid domain of compound **14** with those reported for mestranol allowed us to establish the stereochemistry at the carbinol center, see: a) A. G. J. Sedee, G. M. J. B. van Henegouwen, M. E. de Vries, C. Erkelens, *Steroids* **1985**, *45*, 101; b) M. I. Choudhary, S. G. Musharraf, Z. A. Siddiqui, N. T. Khan, R. A. Ali, Atta-Ur-Rahman, *Chem. Pharm. Bull.* **2005**, *53*, 1011.

[21] G. Savona, M. P. Paternostro, F. Piozzi, B. Rodríguez, *Tetrahedron Lett.* **1979**, *20*, 379.

[22] G. Domínguez, M. C. de la Torre, B. Rodríguez, *J. Org. Chem.* **1991**, *56*, 6595.

[23] A full account of the addition of organolithium reagents to 19-acetylgnaphalin and related compounds will be disclosed in due course.

[24] The ^{13}C NMR spectra of derivatives **16** and **17** are devoid of signals attributable to the carbonyl groups, showing instead signals due to new methyne carbons geminal to the oxygen atom (**16**: $\delta_{C\text{-}6}=73.8$; **17**: $\delta_{C\text{-}6}=74.2$ ppm).

[25] Concerning the stereochemical outcome of the reaction, it has to be mentioned that the signals of the H_{18B}-*endo* protons are shifted to low field (**16**: $\delta_{H-18B}=4.66$; **17**: $\delta_{H-18B}=4.64$ ppm) with respect to the 6α-hydroxy derivative teucjaponin B ($\delta_{H-18B}=3.25$ ppm) as a consequence of the triple-bond effect of the substituent at the 6β-axial position. See: J. Fayos, F. Fernández-Gadea, C. Pascual, A. Perales, F. Piozzi, M. Rico, B. Rodríguez, G. Savona, *J. Org. Chem.* **1984**, *49*, 1789. The deshielding effect of the β-alkyne group is stronger than the effect of a C-6β-hydroxyl group as in teucjaponin A, the H_{18B} signal of which appeared at $\delta=3.78$ ppm). See: G. Y. Papanov, P. Y. Malakov, *Phytochemistry* **1983**, *22*, 2787.

[26] For NMR data of related derivatives, see: D. V. C. Awang, B. A. Dawson, M. Girard, A. Vincent, I. Ekiel, *J. Org. Chem.* **1990**, *55*, 4443.

[27] The ^{1}H NMR spectra of precursors **12**, **13**, and **14** each featured a singlet at $\delta=3.05$–3.07 ppm attributable to the alkynyl proton. As expected, these signals were no longer seen in the spectra of the corresponding dimers **21**, **22**, and **23**.

[28] The ^{13}C NMR signals corresponding to the terminal alkynyl carbons in precursors **17**, **19**, and **20** at $\delta=78.3$, 71.0, and 73.2 ppm are replaced by signals attributable to the new quaternary sp carbons in **24**, **25**, and **26** at $\delta=74.4$, 67.6, and 68.6 ppm, respectively.

[29] It should be noted that compounds **29b** and **30b** are new bioorganometallic derivatives, which have a ferrocene–triazole tether joining the two natural fragments. For the use of ferrocene derivatives in bioorganometallic chemistry, see: a) N. Metzler-Nolte, M. Salmain, "The Bioorganometallic Chemistry of Ferrocene", in *Ferrocene Ligands, Materials and Biomolecules* (Ed.: P. Stepnicka), Wiley-VCH, Weinheim, **2008**, pp. 499–639. A recent example: b) L. Tebben, B. Bussmann, M. Hegemann, G. Kehr, R. Fröhlich, G. Erker, *Organometallics* **2008**, *27*, 4269, and references therein.

[30] The ^{1}H and ^{13}C NMR spectra of dimers **29a–c**, **30a,b**, and **31** were almost identical to those of their precursors, except for the absence of the alkynyl proton signal and the appearance of signals attributable to the tether and the newly formed triazole rings.

[31] No traces of montanin A were detected in the experiments carried out in the course of this work. See ref. [22].

[32] As in the case of the mestranol and reserpine dimers, the ^{1}H NMR spectra of the 19-acetylgnaphalin dimers **32a**, **32b**, and **33** showed a single set of signals for the two natural product fragments, as expect-

ed for molecules having a C_2 symmetry axis. Consequently, the ^{1}H and ^{13}C NMR spectra are almost identical to those of their precursors **16** and **17**, except for the disappearance of the alkynyl proton signal and the appearance of signals attributable to the tether and the newly formed triazole rings. ESI mass spectra for dimers **32a**, **32b**, and **33** showed signals at $m/z = 1069$, 1153, and 1270, corresponding to the respective $[M+H]^+$ ions, in agreement with the proposed structures.

[33] For dimeric compounds as ligands for proteins, see: a) P. A. Clemons, *Curr. Opin. Chem. Biol.* **1999**, *3*, 112; b) S. T. Diver, S. L. Schreiber, *J. Am. Chem. Soc.* **1997**, *119*, 5106; c) K. C. Nicolaou, R. Hughes, S. Y. Cho, N. Wissinger, C. Smethurst, R. Enderman, *Angew. Chem.* **2000**, *112*, 3981; *Angew. Chem. Int. Ed.* **2000**, *39*, 3823; for reviews on dimeric steroids, see: d) L. Nahar, A. B. Turner, *Curr. Med. Chem.* **2007**, *14*, 1349; e) Y. X. Li, J. R. Dias, *Chem. Rev.* **1997**, *97*, 283; for ring-connected dimeric steroids, see: f) V. C. Edelsztein, P. H. Di Chenna, G. Burton, *Tetrahedron* **2009**, *65*, 3615; g) J. F. Templeton, H. Magjier-Baranowska, K. Marat, *Steroids* **2000**, *65*, 219; h) M. DellaGreca, M. R. Iesce, L. Previtera, F. Temussi, A. Zarrelli, C. A. Mattia, R. Puliti, *J. Org. Chem.* **2002**, *67*, 9011; for C–C-connected dimeric steroids, see: i) J. W. Morzycki, S. Kalinowski, Z. Lotowski, J. Rabiczko, *Tetrahedron* **1997**, *53*, 10579.

[34] The synthesis of some star-shaped amphiphilic derivatives of cholic acid using a click reaction has recently been reported: a) J. Luo, Y. Chen, X. X. Zhu, *Synlett* **2007**, 2201; for a recent review on the use of bile acids in synthesis, supramolecular/materials chemistry, and nanoscience, including molecular umbrellas, see: b) Nonappa, U. Maitra, *Org. Biomol. Chem.* **2008**, *6*, 657.

[35] Hybrid macrocyclic scaffolds based on steroids are of special interest due to their structural pre-organization and flexibility; see: a) A. L. Sisson, J. P. Clare, A. P. Davis, *Chem. Commun.* **2005**, 5263; b) A. P. Davis, R. S. Wareham, *Angew. Chem.* **1999**, *111*, 3160; *Angew. Chem. Int. Ed.* **1999**, *38*, 2978; c) P. Wallimann, T. Marti, A. Fürer, F. Diederich, *Chem. Rev.* **1997**, *97*, 1567; d) J. Tamminen, E. Kolehmainen, *Molecules* **2001**, *6*, 21.

[36] It is known that kinetically controlled processes frequently lead irreversibly to the kinetic and statistical distribution of products, including a collection of linear/cyclic oligomers and polymers of different chain lengths, thus inevitably resulting in poor yields of the desired macrocyclic structures. This is in contrast with the reversible reactions that form macrocycles under equilibrium conditions. In these cases, the thermodynamic stability allows the preparation of the macrocyclic target molecule, overcoming the formation of undesired by-products (*dynamic covalent chemistry* (DCC)), see: W. Zhang, J. S. Moore, *Angew. Chem.* **2006**, *118*, 4524; *Angew. Chem. Int. Ed.* **2006**, *45*, 4416.

[37] M. J. Cloninger, H. W. Whitlock, *J. Org. Chem.* **1998**, *63*, 6153.

[38] The ^{13}C NMR spectrum of semicavity **43** featured three signals corresponding to the internal alkynyl carbons at $\delta = 87.5$, 74.8, and 70.9 ppm and a signal at $\delta = 74.1$ ppm attributable to the terminal alkynyl carbons. In contrast, the ^{13}C NMR spectra of compounds **41** and **44** showed four signals corresponding to the internal sp carbons at $\delta = 83.0$, 74.5, 71.1, and 69.8 ppm and at $\delta = 83.4$, 74.9, 71.1, and 70.4 ppm, respectively, confirming their identity as closed oligomeric structures of the precursor **43**.

[39] A cholic acid-based triply-bridged cyclophane showing moderate binding of organic guest molecules has been reported, see: S. Kohmoto, D. Fukui, T. Nagashima, K. Kishikawa, M. Yamamoto, K. J. Yamada, *J. Chem. Soc. Chem. Commun.* **1996**, 1869.

[40] Tripodal species containing a trisubstituted triethylbenzene core exhibit a preference of 10–15 kJ mol^{-1} for an alternating (3-up, 3-down) conformation and, therefore, are partially pre-organized, with the three arms oriented in the same direction. See: K. J. Wallace, W. J. Belcher, D. R. Turner, K. F. Syed, J. W. Steed, *J. Am. Chem. Soc.* **2003**, *125*, 9699, and references therein.

[41] The ^{13}C NMR spectrum of precursor **46b** featured one signal corresponding to the internal alkynyl carbons at $\delta = 87.5$ ppm and one signal at $\delta = 74.0$ ppm attributable to the terminal alkynyl carbons. No significant simplification of the signals of compound **47** was observed in the ^{1}H and ^{13}C NMR spectra recorded in [D$_6$]DMSO at 90 °C.

[42] A. Vacca, C. Nativi, M. Cacciarini, R. Pergoli, S. Roelens, *J. Am. Chem. Soc.* **2004**, *126*, 16456.

[43] High-dilution techniques using a syringe pump did not improve this result. CuCl/CuCl$_2$-Py afforded the target molecule in only 6% yield, while Hay conditions (CuCl/TMEDA/O$_2$, RT) did not generate the target product.

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