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A Straightforward Synthesis of Tetrameric Estrone-Based Macrocycles

Pedro Ramírez-López,*,† María C. de la Torre,*,† Hector E. Montenegro,†,‡ María Asenjo,† and Miguel A. Sierra*,‡

Instituto de Química Orgánica, Consejo Superior de Investigaciones Científicas (CSIC), Juan de la Cierva 3, 28006-Madrid, Spain, and Departamento de Química Orgánica, Facultad de Química, Universidad Complutense, 28040-Madrid, Spain

pedror@iqog.csic.es; ctorre@iqog.csic.es; sierraor@quim.ucm.es

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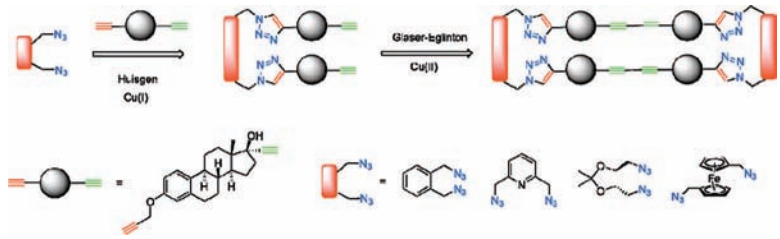
ABSTRACT



A straightforward approach to macrocycles having four estrone-derived nuclei by the sequential Cu-catalyzed Huisgen azide−alkyne cycloaddition−Glaser−Eglington Cu homocoupling has been developed. Due to its efficiency and simplicity, this sequence is useful for application to different natural product scaffolds.

Cu-promoted alkyne coupling[1] and Huisgen 1,3-dipolar cycloaddition chemistry[2] have been widely applied to the preparation of macrocycles.[3,4] Nevertheless, since most of these coupling-based methods are kinetically controlled processes, they frequently lead irreversibly to the kinetic and statistical distribution of products, including a large collection of linear/cyclic oligomers and polymers of different chain length, resulting inevitably in poor yields of the desired macrocyclic structures. This fact contrasts with dynamic covalent chemistry (DCC), the reversible nature of which overcomes the formation of undesired linear/cyclic structures allowing the preparation of the macrocyclic target molecule.[3] In this context, during our search for new macrocyclic entities, we used the DCC approach to prepare polymetallic natural product based macrocycles employing the Nicholas reaction[5] and the reversible Michael addition of bisamines to bisalkyne tethered group 6 biscarbene complexes to form di- and tetrametallic macrocycles in a single step (Figure 1).[6]

The common target of this research was to generate new macrocyclic bio-organometallic scaffolds as well as co-

† Consejo Superior de Investigaciones Científicas (CSIC).
‡ Universidad Complutense.

(1) (a) Hay, A. S. *J. Org. Chem.* **1962**, *27*, 3320. For an overview on acetylenic homocoupling, see: (b) Siemsen, P.; Livingston, R. C.; Diederich, F. *Angew. Chem., Int. Ed.* **2000**, *39*, 2632, and references therein.

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(3) Zhang, W.; Moore, J. S. *Angew. Chem., Int. Ed.* **2006**, *45*, 4416.

(4) Recent examples on the use of the Huisgen catalyzed Cu azide−alkyne cycloaddition to close macrocyclic rings: (a) Aher, N. G.; Pore, V. S.; Patil, S. P. *Tetrahedron* **2007**, *63*, 12927. (b) Bodine, K. D.; Gin, D. Y.; Gin, M. S. *J. Am. Chem. Soc.* **2004**, *126*, 1638. (c) Bodine, K. D.; Gin, D. Y.; Gin, M. S. *Org. Lett.* **2005**, *7*, 4479. (d) Turner, R. A.; Oliver, A. G.; Lokey, R. S. *Org. Lett.* **2007**, *9*, 5011. (e) Bock, V. D.; Perciaccante, R.; Jansen, T. P.; Hiemstra, H.; van Maarseveen, J. H. *Org. Lett.* **2006**, *8*, 919. (f) Laurent, B. A.; Grayson, S. M. *J. Am. Chem. Soc.* **2006**, *128*, 4238.

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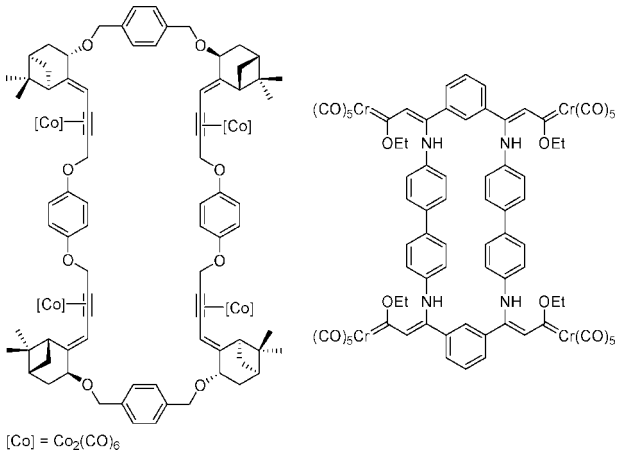
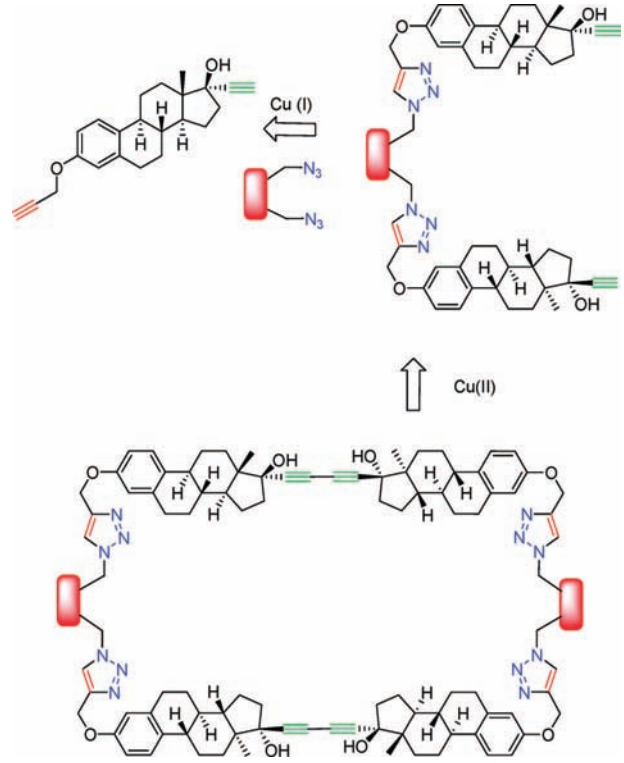


Figure 1. Some polymetallic macrocycles prepared using the DCC cyclooligomerization approach.

valently connected polymetallic macrocyclic rings (in contrast with macrocycles joined through a more flexible M−C bond)[7] to study the long-range interaction between metallic centers.

In contrast with this previous work and according to literature precedents, the sequential building of a macrocycle in a limited number of steps will face relative overall low yields and contamination with a large collection of linear/cyclic oligomers and polymers of different chain length.[3] However, the use of rigid steroid scaffolds may help to overcome these problems. In fact, this rigidity makes steroids exceptional building blocks for the synthesis of steroid-based macrocyclic molecules.[8] We report herein a straightforward cyclodimerization of a bissteroid scaffold, prepared employing a "Click" reaction[9] on a bisalkyne steroid, by using a Cu-promoted Glaser−Eglinton homocoupling to furnish in good overall yields a series of chiral, highly symmetric tetrameric estrone-derived macrocycles (Scheme 1).

Scheme 1. Synthetic Strategy for the Cu-Catalyzed Synthesis of Estrone-Based Macrocycles



Estrone **1** was propargylated at the oxygen and subsequently reacted with lithium TMS-acetylide, using standard methodology to form **2**, which was submitted to reaction with bisazides **3a**−**f**. The resulting dimers **4a**−**f** were isolated in 72−88% yields (Scheme 2), demonstrating the exceptional efficiency of the Cu-catalyzed Huisgen reaction.[10] Aromatic (**4a**−**c**), heteroaromatic (**4d**), aliphatic (**4e**), and ferrocenyl (**4f**) derived azides were fully compatible with this process.[11]

Having prepared half of the cavity, the TMS-group of the alkyne of compounds **4** was removed (TBAF, THF), and the terminal diyne **5** was submitted to the Glaser−Eglinton coupling ($Cu(OAc)_2 \cdot H_2O$/MeCN,Py).[12] The result of this coupling strongly depends on the nature of the tether joining both steroid nuclei. Thus, while compounds **5a** and **5d**,**f** furnished the desired macrocycles **6**, having four steroid nuclei, four triazole, and two 1,3-diyne linkers disposed

(8) The review by Li and Dias compiles most of the different structural types of steroid-based architectures reported: (a) Li, Y.; Dias, J. R. *Chem. Rev.* **1997**, *97*, 283. (b) Wallimann, P.; Marti, T.; Fürer, A.; Diederich, F. *Chem. Rev* **1997**, *97*, 1567. For the use of esteroids in the preparation of cholaphanes and cholaphane-based macrocycles, see: (c) Tamminen, J.; Kolehmainen, E. *Molecules* **2001**, *6*, 21. (d) Rivera, D. G.; Wessjohann, L. A. *Molecules* **2007**, *12*, 1890. (e) Virtanen, E.; Kolehmainen, E. *Eur. J. Org. Chem.* **2004**, 3385.

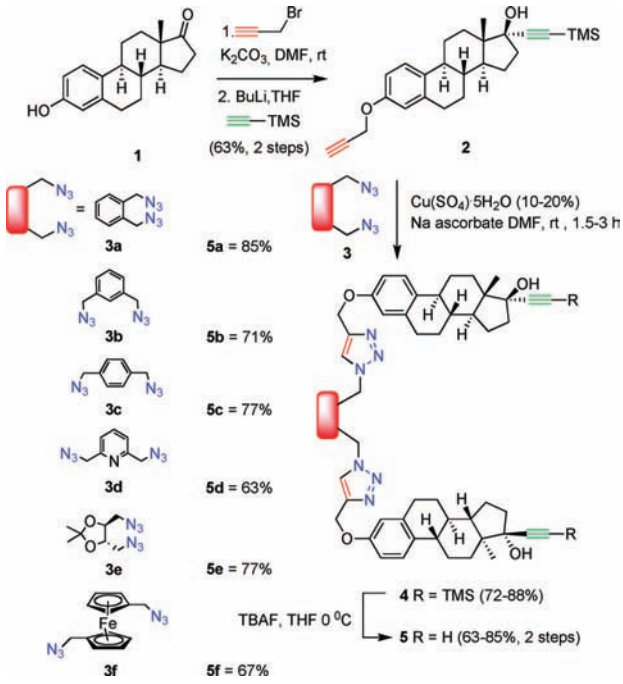
(9) (a) Kolb, H. C.; Finn, M. G.; Sharpless, K. B. *Angew. Chem., Int. Ed.* **2001**, *40*, 2004. The head to tail cyclodimerization of peptides by the copper(I)-catalyzed azide−alkyne reaction has been reported. See: (b) Punna, S.; Kuzelka, J.; Wang, Q.; Finn, M. G. *Angew. Chem., Int. Ed.* **2005**, *44*, 2215. The following reference contains a nice selection of the state of the art on the copper(I)-catalyzed azide−alkyne reaction: (c) Rodionov, V. O.; Presolski, S. I.; Gardinier, S.; Lim, Y. H.; Finn, M. G. *J. Am. Chem. Soc.* **2007**, *129*, 12696.

(10) The synthesis of compound **4a** is representative: A mixture of diazide **3a** (82.4 mg, 0.438 mmol, 1.0 equiv), alkyne **2** (356.6 mg, 0.877 mmol, 2.0 equiv), sodium (*L*)-ascorbate (17.4 mg, 0.088 mmol, 0.2 equiv), and $CuSO_4 \cdot 5H_2O$ (11.0 mg, 0.044 mmol, 0.1 equiv) in DMF (10 mL) was stirred under Ar at rt for 3 h. The reaction was quenched with water at 0 °C and allowed to reach rt. The mixture was extracted with AcOEt (3 × 20 mL), and the organic extracts were washed with water (2 × 20 mL) and once with brine (20 mL). The organic layer was dried over $MgSO_4$ and filtered, and the solvent was removed under vacuum. The resulting white solid was purified through a short pad of SiO_2 (Hex/AcOEt 2:1 to 1:3) to yield **4a** as a white solid (384.5 mg, 88%). M.p. 126−128 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.48 (s, 2H), 7.40−7.36 (m, 2H), 7.27−7.25 (m, 2H), 7.20 (d, J = 8.7 Hz, 2H), 6.75 (dd, J_1 = 8.7 Hz, J_2 = 2.4 Hz, 2H), 6.67 (d, J = 2.4 Hz, 2H), 5.62 (s, 4H), 5.13 (s, 4H), 2.90−2.73 (m, 4H), 2.41−1.21 (m, 28H), 0.86 (s, 6H), 0.17 (s, 18H). ^{13}CNMR (75 MHz, $CDCl_3$) δ 156.0 (C), 145.0 (C), 138.0 (C), 133.1 (C), 130.4 (CH), 129.8 (CH), 126.4 (CH), 122.8 (CH), 122.7 (C), 114.7 (CH), 112.2 (CH), 109.5 (C), 89.9 (C), 80.0 (C), 62.0 ($2CH_2$), 51.2 ($3CH_2$), 49.5 (CH), 47.1 (C), 43.7 (CH), 39.3 (CH), 38.9 (CH_2), 32.8 (CH_2), 29.7 (CH_2), 27.2 (CH_2), 26.4 (CH_2), 22.8 (CH_2), 12.7 (CH_3), 0.0 (CH_3). IR (KBr) ν_{max} 3435, 3139, 2160, 1609, 1498, 1456, 1250, 1047, 843 cm^{-1}. $[\alpha]_D^{30}$ −15.15 (*c* 0.858, $CHCl_3$). MS (ES) *m/z* 1001.3 $[M + H]^+$. Anal. Calcd. for $C_{60}H_{76}N_6O_4Si_2$: C, 71.96; H, 7.65; N, 8.39. Found: C, 72.23; H, 7.83; N, 8.13.

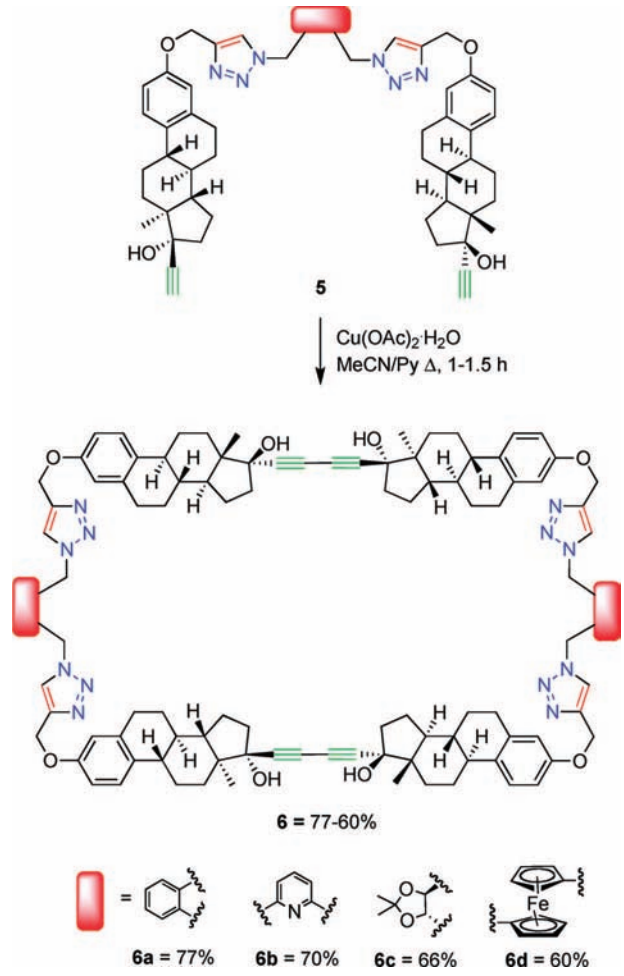
(11) The structure of all new compounds fully satisfies their spectroscopic data. See the Supporting Information.

(12) Cloninger, M. J.; Whitlock, H. W. *J. Org. Chem.* **1998**, *63*, 6153.

Scheme 2. Synthesis of Semicavities **4** and **5**



Scheme 3. Cyclooligomerization Reactions to Prepare Estrone-Based Macrocycles **6**



symmetrically (it should be noted that the structures have a macrocyclic symmetry plane) in good to excellent yields,[13] compounds **5b** and **5c** did not yield the desired macrocycles (Scheme 3).

The structure of highly symmetric compounds **6** was ascertained by spectroscopic means (NMR studies and MS analysis). The ^{1}H and ^{13}C NMR for macrocycles **6** account for one-fourth of the molecule and were almost identical to those of the corresponding dimers **5a** and **5d**,**f**, except for the presence of signals attributable to the symmetrically 1,4-disubstituted-1,3-dialkyne bridge and the lack of the signals corresponding to the terminal alkyne moiety. The possible formation of highly symmetric [2 + 2], [3 + 3], or [4 + 4] products was discarded by ESI−MS. Thus, compound **6a** showed a signal at *m*/*z* 1732.8 corresponding to $[M + Na]^+$; compound **6b** showed a signal at *m*/*z* 1713.2 corresponding to $[M + H]^+$; and compound **6c** showed two signals at *m*/*z* 1780.2 and *m*/*z* 1758.7 attributable to the ions $[M + Na]^+$ and $[M + H]^+$, respectively. Finally, compound **6d** showed a molecular peak at *m*/*z* 1926.9 $[M + H]^+$ in agreement with the proposed macrocyclic structure. Therefore, the formation of lower or higher macrocyclic homologues was discarded.

The behavior of semicavities **5b**,**c** contrasts with those of compounds **5a** and **5d** having 1,2-phenyl and 2,6-pyridyl bridges, respectively. Compounds **5b**,**c** gave rise to the formation of variable amounts of insoluble polymeric material, which may be attributed to the relative *m*- and *p*-disposition of the bridging aromatic ring, compared to the *o*-disposition of the compound **5a**. The ability of compound **5d** to form the macrocyclic ring may be attributed to the chelating effect of the pyridine and triazole nitrogens which may template the Cu-promoted alkyne dimerization.[14]

It should be noted that compound **6d** has two ferrocene nuclei in its macrocyclic structure. The simultaneous presence

(13) The synthesis of macrocycle **6a** is representative: To a mixture of dry pyridine (7 mL)/CH_3CN (21 mL), heated at reflux for 1 h, dimer **5a** (50.0 mg, 0.058 mmol, 1.0 equiv) and $Cu(OAc)_2{\cdot}H_2O$ (57.9 mg, 0.290 mmol, 5.0 equiv) were successively added. After refluxing for 1 h, the reaction mixture was allowed to reach rt, quenched with ice, diluted with AcOEt (40 mL), and washed with H_2O (3 × 50 mL). The organic layer was dried over anhydrous Na_2SO_4, and solvents were removed under vacuum. The resulting residue was purified through a short pad of SiO_2 (10.2 cm, Hex/AcOEt 1:2 to 1:4) to yield **6a** as a white solid (38.2 mg, 77%). M. p. = 260−262 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.47−7.43 (m, 4H), 7.34 (s, 4H), 7.35−7.32 (m, 4H), 7.04 (d, J = 8.7 Hz, 4H), 6.66 (dd, J_1 = 8.7 Hz, J_2 = 2.4 Hz, 4H), 6.58 (d, J = 2.4 Hz, 4H), 5.65 (s, 8H), 5.23 (s, 8H), 2.89−2.67 (m, 8H), 2.44−2.35 (m, 8H), 2.19−2.02 (m, 8H), 1.96−1.27 (m, 40H), 0.95 (s, 12H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 155.4 (C), 145.3 (C), 137.7 (C), 132.9 (C), 132.3 (C), 130.6 (CH), 129.9 (CH), 126.0 (CH), 122.5 (CH), 115.3 (CH), 112.0 (CH), 84.5 (C), 80.4 (C), 70.1 (C), 61.7 (CH_2), 51.1 (CH_2), 49.9 (CH), 48.4 (C), 44.1 (CH), 39.1 (CH), 38.5 (CH_2), 33.1 (CH_2), 29.6 (CH_2), 27.3 (CH_2), 26.3 (CH_2), 22.8 (CH_2), 12.8 (CH_3). IR (KBr) ν_{max} 3436, 2929, 1609, 1498, 1452, 1250, 1232, 1051, 1023 cm^{-1}. $[\alpha]_D^{30}$ −62.72 (*c* 0.220, $CHCl_3$). MS (ES) *m*/*z* 1732.8 $[M + Na]^+$. Anal. Calcd. for $C_{108}H_{116}N_{12}O_8$: C, 75.85; H, 6.84; N, 9.83. Found: C, 75.54; H, 7.01; N, 9.62.

(14) (a) Cristau, H.-J.; Cellier, P. P.; Spindler, J.-F.; Taillefer, M. *Chem.−Eur. J.* **2004**, *10*, 5607. (b) Jia, W. L.; McCormick, T. M.; Tao, Y.; Lu, J.-P.; Wang, S. *Inorg. Chem.* **2005**, *44*, 5706. (c) McCormick, T. M.; Liu, Q.; Wang, S. *Org. Lett.* **2007**, *9*, 4087.

of four steroid nuclei and two iron metal nuclei makes macrocycle **6d** a bio-organometallic derivative.[15] Reported examples of this class of compounds are scarce, and their biological relevance remains to be determined.

To conclude, the straightforward access to macrocycles having four estrone-derived nuclei by the sequential Cu-catalyzed Huisgen azide−alkyne cycloaddition−Glaser−Eglington Cu-homocoupling has been developed. The approach uses two differentiated triple bonds attached to the steroid nucleus; it is tunable in both the tether and the scaffold; and due to its efficiency and simplicity, it is useful for application to different natural product scaffolds. The success of this approach probably rests in the rigidity of the estrone nucleus, which overcomes the kinetically unfavorable cyclodimerization process by providing the preorganization required to avoid the formation of linear oligomers. Progress in these laboratories to achieve the synthesis of higher macrocyclic homologues as well as to study the behavior of these chiral rich cavities is underway.

(15) For an overview of this field, see: (a) Dagani, R. *Chem. Eng. News.* **2002**, *80*, 23–29. (b) Special issue on bioorganometallic chemistry: *J. Organomet. Chem.* **1999**, *589*, 1.

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Supporting Information Available: Full experimental and listed spectroscopic data for the compounds **3**, **4**, **5**, and **6** described in the paper as well as copies of their ^{1}H and ^{13}C NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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