Synthesis of polymetallic macrocyclic terpene-derived hybrids†

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Terpene alkyne systems act as templates in the preparation of natural product hybrids and in macrocyclic structures having up to four terpene units and eight Co-atoms, which are built by using the Nicholas reaction.

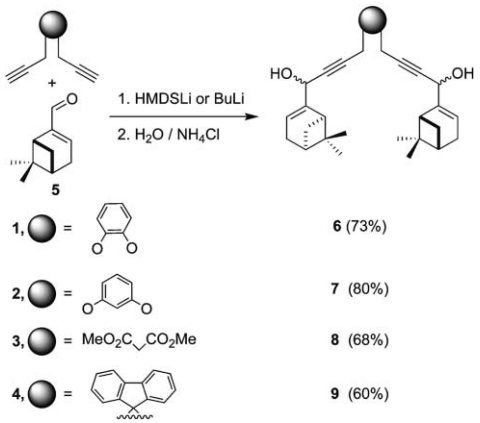
Macrocyclic natural products represent the equilibrium between conformational preorganization and flexibility to achieve optimal binding properties to their biological targets. These intrinsic properties, coupled to the fact that these compounds have very diverse structures, produce remarkable biological activities ranging from the antibacterial erythronolide to the immunosupressant cyclosporine.[1] It has been noted additionally that the incorporation of benzene rings as aryl ethers and biphenyl units in biologically active macrocyclic natural products is very frequent.[2]

The appearance of resistance to some of the most commonly used macrocyclic drugs has launched an extensive program of modification of natural products to surpass this problem.[3] For example, sugar modification in vancomycin has produced new drugs able to inhibit the growth of vancomycin resistant *Staphylococcus aureous*.[4]

An alternative approach in response to the necessity of increasing the structural diversity of available macrocyclic structures is the *de novo* tailored synthesis of macrocycles having natural product moieties.[5] These hybrid compounds may be prepared by developing methodologies based on diversity oriented synthetic strategies,[6] which could produce an almost inextinguishable number of structural types. In this context, we reported recently[7] the suitability of (*R*)-(+)-sclareolide as a template for the diversity oriented synthesis of several hispanane derivatives. We have also demonstrated the usefulness of (1*R*)-(–)-myrtenal in the preparation of sophisticated terpene–terpene heterohybrids using the Nicholas reaction.[8]

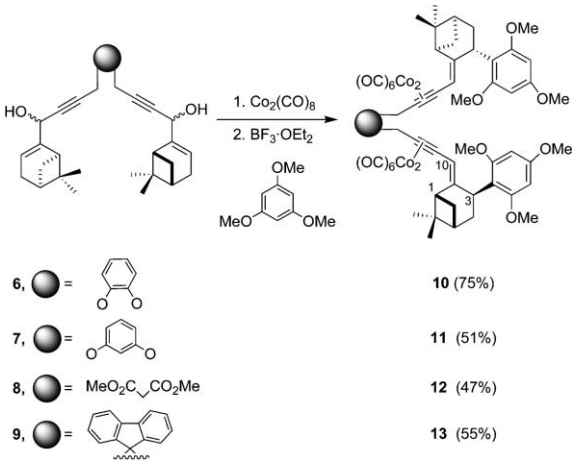
We foresee that the exceptional ability of Co-clusters to stabilize α-carbocations[9] would enable the building of more complex structures. Thus, tethering two terpenes with a diyne spacer would produce structures which would be able, in principle, to experience a double Nicholas reaction, and depending on the electrophilic quencher for these bis-carbocations, open-chain or macrocyclic structures may be accessed.[10] Alkyne hexacarbonyldicobalt complexes have been recently recognised as a new class of potent cytotoxic drugs,[11] and are used as bio-markers for carbonyl-metallo-immuno-assay.[11] Herein is reported the initial results of the synthesis of macrocyclic natural product hybrids containing up to eight Co-atoms.

1,2- and 1,3-(bispropynyloxy)benzene **1** and **2**, 2,2-di(propynyl)-malonate **3** and 9,9-di(prop-2-inyl)fluorene **4** were used as diyne spacers to attach the terpenic structures. Condensation of the lithium salts of compounds **1–4** with (1*R*)-(–)-myrtenal **5** gave the corresponding diols **6–9** as diastereomeric mixtures in good to excellent yields (Scheme 1).



Scheme 1 Preparation of propargylic diterpene-diols **6–9**.

Compounds **6–9** were reacted with $Co_2(CO)_8$ in dry Cl_2CH_2 and submitted to treatment with $BF_3{\cdot}OEt_2$ at −78 °C (compounds **6** and **7**), −20 °C (compound **9**) or 0 °C (compound **8**) in the presence of two equivalents of 1,3,5-trimethoxybenzene. Compounds **10–13** were obtained in all cases in isolated yields higher than 46% and as single stereoisomers (Scheme 2).[12,13]



Scheme 2 Synthesis of aromatic-terpene derivatives having diverse spacers.

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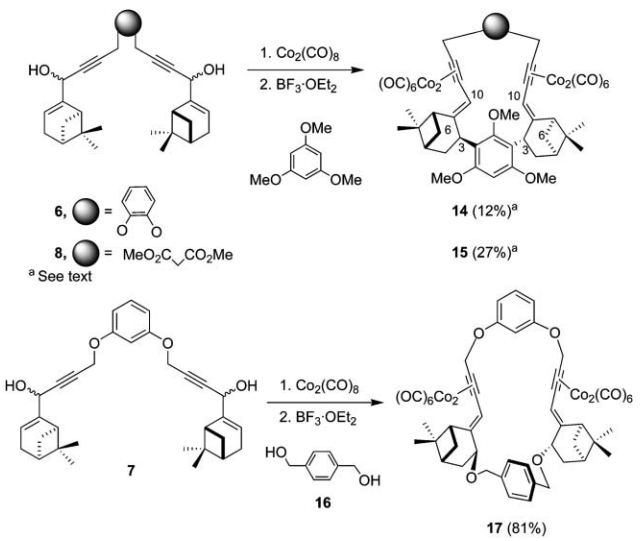
The structures of compounds **10–13** were established on spectroscopic grounds as follows. The ^{1}H and ^{13}C-NMR for compounds **10–13** were almost identical except for the signals corresponding to each diyne spacer. In addition, the ^{1}H and ^{13}C-NMR spectra showed signals for half of each molecule, as expected for the presence of a C_2 symmetry axis. The regio- and stereochemistry of products **10–13** was established by comparison of the chemical shifts of the carbons corresponding to the terpene and the aromatic fragments with those reported for the related hybrids derived from β-pinene.[8] This confirms that the addition of 1,3,5-trimethoxybenzene to the cations derived from **6–9** takes place at carbon C-3 of the terpene fragment by the opposite face to the geminal dimethyl group.

Conditions to close a macrocyclic system through a double Nicholas reaction on 1,3,5-trimethoxybenzene were searched for next. This was achieved by reacting 1 equivalent of compounds **6** and **8** with 1 equivalent of 1,3,5-trimethoxybenzene in the presence of $BF_3{\cdot}OEt_2$ (1 equivalent). Macrocyclic compounds **14–15** were obtained as single diastereoisomers together with compounds **10** and **12** (Scheme 3).



Scheme 3 Synthesis of macrocyclic terpene-derived hybrids.

The structures of compounds **14** and **15** were unambiguously established by comparison of their ^{1}H and ^{13}C-NMR data with the related open chain derivatives **10** and **12**. Firstly, the two terpenic fragments are not equivalent, since two patterns of signals are observed in the ^{1}H and ^{13}C-NMR data for **14** and **15**. In addition, the ^{1}H-NMR showed only one singlet signal, at 6.27 and 6.32 ppm for **14** and **15** respectively, which accounts for one single aromatic proton attributable to the 1,3,5-trimethoxybenzene fragment. This excludes open-chain products like **10–12** which show instead two broad singlet signals (two protons each) corresponding to the two aromatic fragments. The macrocyclic nature of **14** and **15** was clearly established by 2D NMR experiments. As an example, the long range coupling *g*HMBC spectrum, for compound **15**, showed cross-peaks between the H-3 protons of each terpene fragment at 4.67 and 4.21 ppm, and the same aromatic carbon of the 1,3,5-trimethoxybenzene moiety at 160.3 ppm. This observation can only be satisfied by the proposed cyclic structures.

The stereochemistry at the terpenic C-3 positions and at the exocyclic double bonds was determined by nOe experiments. Irradiation of the signals corresponding to the H-3 protons caused an increase in the intensity of the signals corresponding to the olefinic protons H-10 and to the *pro-S* terpenic methyl groups. In accordance with these results, 1,3,5-trimethoxybenzene must have a *syn* relationship with carbon C-6 of both terpene fragments, and the $\Delta^{2(10)}$ double bonds must have *E*-configurations.

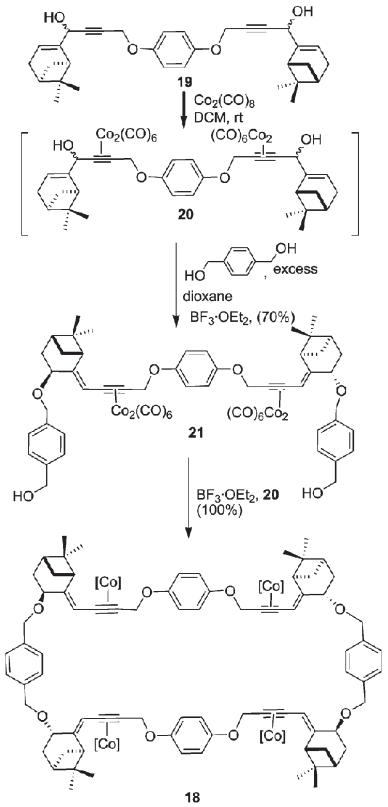
It is clear from the results above that even if 1,3,5-trimethoxybenzene is efficient to produce open-chain double Nicholas products, it is mediocre to promote the ring closure, probably due to the structural stress imposed to the macrocycle.

1,4-Benzenedimethanol **16** was used next as the capping moiety to trap the bis-cation in order to close the macrocyclic ring. Reaction of diol **16** with the $Co_2(CO)_6$-bis-alkyne complex derived from **7** in the presence of $BF_3{\cdot}OEt_2$ formed a single product whose spectroscopic data were fully consistent with the desired macrocycle **17** (Scheme 3). The structure of compound **17** was assigned in the metal-free product. In this case the molecule must have a C_2 axis, since the ^{1}H and ^{13}C-NMR showed signals for half of the molecule. A *g*HMBC cross-peak between H-3 at 4.02 ppm and the methylene carbon at 70.1 ppm, attributable to the nucleophile fragment, established unambiguously that this fragment is connected to the two terpene moieties. The stereochemistry of all the new centers was determined by nOe experiments. Irradiation of the terpenic proton H-3 (δ_H 4.02) caused an increase in the intensity of the signals at δ_H 5.35, 4.37, and 0.63 attributable to the olefinic proton H-10, to one proton of the methylene carbon of the nucleophile, and to the *pro-S* Me-group of the terpenic fragment, respectively.

To further extend the scope of the approach reported herein, macrocycle **18** was prepared in three steps from **19**, which was obtained in 98% yield from 1,4-(bispropynyloxy)benzene and (1*R*)-(−)-myrtenal. $Co_2(CO)_6$-Bis-alkyne complex **20** was generated from **19** and reacted *in situ* with 1,4-benzenedimethanol to provide **21**, which was used to close macrocycle **18**. The structure of **21** was in agreement with its spectroscopic data. Of special value for comparative purposes, are signals due to the three different methylene groups, which appear at 5.15 ppm for the catechol-derived spacer, at 4.63 and 4.46 ppm for the 1,4-benzenedimethanol methylene carbon linked to the terpene, and at 4.68 ppm for the free hydroxymethyl groups.

The Nicholas reaction of **20** with the diol **21** gave a nearly quantitative yield of the octametallamacrocycle **18** as a single stereoisomer (Scheme 4). ^{1}H and ^{13}C-NMR for macrocycle **18** showed signals for half of the molecule, and they are almost identical to compound **21** except for the lack of signals corresponding to the free hydroxymethyl groups. Analogously to macrocycle **17**, a *g*HMBC cross-peak between the terpenic proton H-3 at 4.06 ppm and the methylene carbon at 69.3 ppm, of the 1,4-benzenedimethanol moiety, confirms structure **18** as the Nicholas reaction product between the cobalt complex **20** and diol **21**.

Finally, to stress the efficiency of this methodology, the assembly of **18** was effected in a single step from template **19** by reaction with 1 equivalent of 1,4-benzenedimethanol under the conditions used for the stepwise procedure. Macrocycle **18** was obtained as a single stereoisomer and in quantitative yield. The bias of bis-cations derived from **20** for self assembly may be explained from the rigidity imposed by the



Scheme 4 Synthesis of macrocycle **18**.

tricentred-carbocation-cluster system of these cations, which may preorganize the reagents (Scheme 4).

To discard the possibility of obtaining compounds analogous to **17** in this process, we submitted **21** to the standard reaction conditions, but in the absence of the capping moiety. A mixture of unreacted starting material and other compounds was obtained. Neither **18** nor traces of an analogous compound to **17** were observed.

To conclude, the ability of terpene alkyne systems to act as templates in the preparation of natural product hybrids and in macrocyclic structures having up to four terpene units, up to four aryl ether units and up to eight Co-nuclei has been demonstrated. Furthermore, the assembly of these macrocyclic octametallic natural product derivatives can be effected in a single step from the initial template. Work to extend this methodology to the auto-assembly of more complex structures as well as to prepare diverse macrocyclic natural product derived heterohybrids is underway in our laboratories.

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13 Compound **8** also provided **15** under these conditions, in 13% yield.