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Porphyrinoids

Bicyclo[1.1.1]pentane Embedded in Porphyrinoids**

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Dedicated to Professor Jonathan L. Sessler

Abstract: We report a two-step approach to obtain synthetically versatile bicyclo[1.1.1]pentane (BCP) derivatives using Grignard reagents. This method allows the incorporation of BCP units in tetrapyrrolic macrocycles and the synthesis of a new class of calix[4]pyrrole analogues by replacing two bridging methylene groups with two BCP units. In addition, a doubly N-confused system was also formed in the presence of electron-withdrawing substituents at the BCP bridgeheads. The pyrrole rings in BCP containing macrocycles exist in 1,3-alternate or αβαβ conformations, as observed from single-crystal X-ray diffraction analyses and 2D NMR spectroscopy.

Bioisosteres are chemical moieties that can be substituted for common functional groups or linkages; for example, bicyclo[1.1.1]pentane offers a linear connection similar to *para*-phenylene, and this replacement can inhibit usual aggregation and metabolic inactivation in drugs.[1] BCP derivatives are also used as liquid crystals, molecular rotors, and as spacer unit in chromophoric arrays.[2] To meet the increased demand for BCPs in pharmaceutical and material sciences several research groups are developing synthetic protocols for novel BCP building blocks. Most BCP derivatives have been synthesized via ring opening of [1.1.1]propellane followed by multi-step chemical transformation to append functional groups at bridgehead positions.[3] However, the ring opening strategy is mainly limited to C–X (X = S, I, N, P, etc.) bond formation and cannot be employed to generate C–C bonds at both bridgehead positions simultaneously.[3d–g] Other popular approaches to derivatize BCP rely on converting the carboxylic acid group (**1**) into redox-active esters (**2**) followed by Fe or photoredox cross-coupling reactions (Figure 1a).[4] Despite the current development, practical access to useful BCP building blocks is limited due to lengthy and complex chemical transformation protocols. Therefore, an inexpensive and straightforward strategy to incorporate 1,3-bis α-quaternary groups at the bridgehead positions of BCP remains unexplored.

Since its discovery, Grignard reagents have been extensively used in industrial production.[5] Organomagnesium reagents show high reactivity and their chemoselectivity can be enhanced by transmetalation.[6] To this end, Knochel and co-workers reported a modified synthetic protocol to access 1,3-bisaryl substituted BCPs. The authors used a conventional route, including the reaction of [1.1.1]propellane with

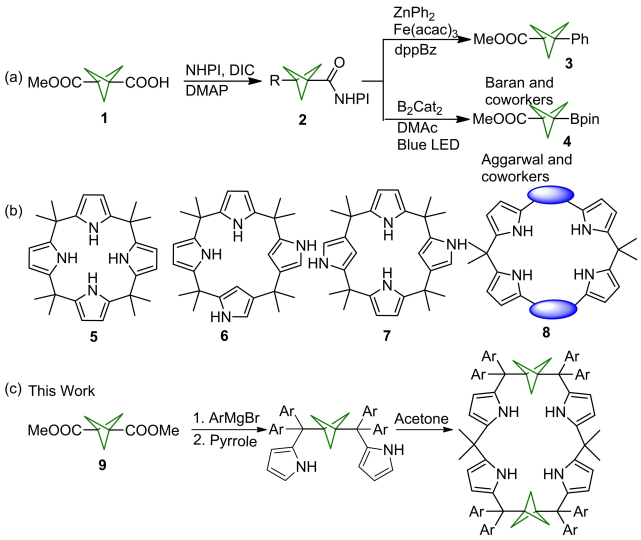

Figure 1. a) Synthetic pathways to functionalize BCP bridgehead positions; b) structures of calix[4]pyrrole derivatives; c) schematic summary of current work.

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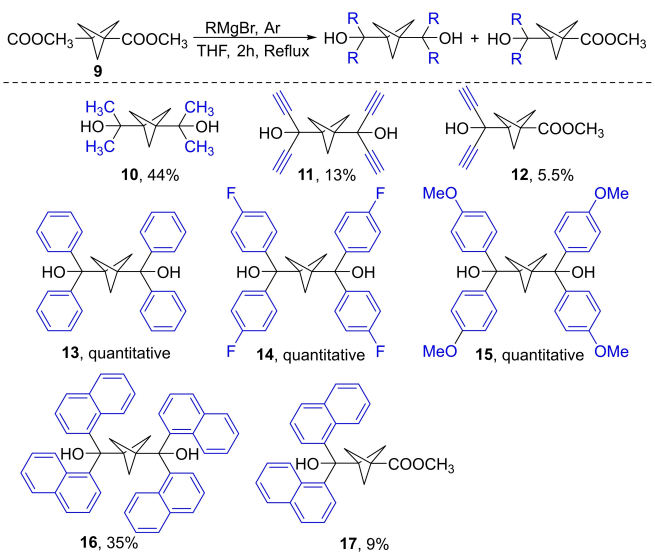
ArMgX followed by transmetallation with zinc. The Zn derivative undergoes Negishi coupling reactions to access 1,3-bisaryl BCP derivatives.[7]

Given the stability of the BCP scaffold towards Grignard reagents, we envisaged that a reaction between alkyl/arylmagnesium halide and dimethyl bicyclo[1.1.1]pentane-1,3-dicarboxylate can introduce the BCP moiety into organic target molecules in a predictable way. To this end, we treated a variety of Grignard reagents with dimethyl bicyclo-[1.1.1]pentane-1,3-dicarboxylate to yield BCP-dimethanol derivatives. Furthermore, the diols were reacted with pyrrole followed by calix[4]pyrrole synthesis. Calix-[4]pyrroles (**5–8**) are macrocycles containing four pyrrole rings linking via four sp^3 carbon atoms (Figure 1b).[8] Calix-[4]pyrroles exhibit structural flexibility and adopt four possible conformations, i.e. conical, partial conical, 1,2-alternating, and 1,3-alternating in solution. The replacement of the methylene groups with other organic subunits can control the flexibility and alter structural properties of the resulting compounds.[9] In this context, the incorporation of rigid, bulky and non-conjugated σ-bonded BCP(s) into the calix[4]pyrrole backbone provides spatial organization of the substituents, resulting in preorganized calix[4]pyrrole derivative.

We started this study with a reaction of dimethyl bicyclo[1.1.1]pentane-1,3-dicarboxylate (**9**) and four equiv. methylmagnesium bromide in THF under reflux conditions. The reaction worked well and the desired product **10** was obtained in 44 % yield. A similar reaction of ethynylmagnesium bromide with **9** proved more difficult with large amounts of starting material evidenced in the ^{1}H NMR of the crude reaction mixture. Increasing the equivalents of Grignard reagent slightly improved the yield and **11** was obtained in 13 % yield accompanied by traces of **12**. The overall yield of products (**11** and **12**) remained low in this case. Following, we attempted a reaction of vinylmagnesium bromide with **9**, resulting in decomposition of the starting material. Due to the limited success with alkyl magnesium bromides, we employed aryl magnesium bromides for further reactions. Reaction of phenylmagnesium bromide with **9** afforded the quantitative formation of compound **13**. To study the scope of the synthetic protocol we synthesized representative derivatives (**14–16**) bearing 4-fluorophenyl, 4-methoxyphenyl and 1-naphthyl substituents on the bridge-head position of the BCP moiety. In the case of the 1-naphthyl derivative, **17** was also obtained as a side product (Scheme 1).

Carbinols are suitable precursors for porphyrins[10] and thus reactions of the BCP-biscarbinols with pyrroles were the next target. Initially, treatment of compound **10** with excess pyrrole in the presence of $BF_3{\cdot}OEt_2$ resulted only in degradation of the precursor. A similar result was observed for **11**.

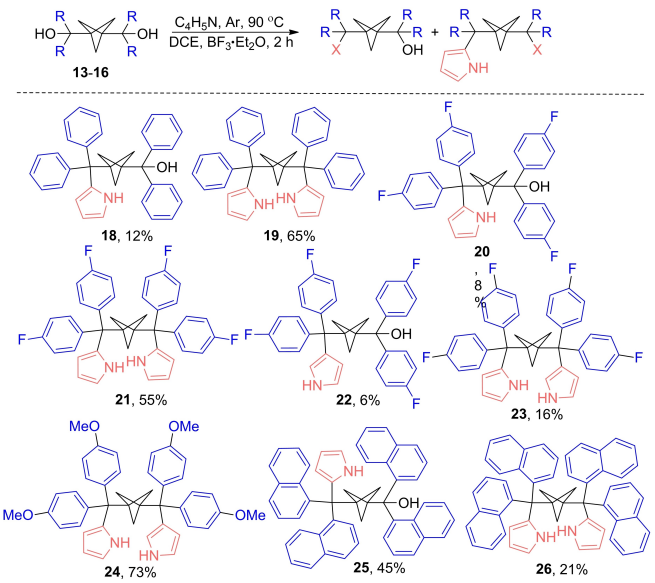
A reaction of compounds **13–16** with excess pyrrole in the presence of $BF_3{\cdot}OEt_2$ at RT did not proceed well and only minor quantities of products were obtained. The lower yields were attributed to the poor solubility of the diols **13–16** in pyrrole. Next, a mixture of pyrrole and BCP-diol **13** was dissolved in 1,2-DCE and heated at 90 °C in the



Scheme 1. Synthesis of BCP diol derivatives **10–17**.

presence of $BF_3{\cdot}OEt_2$ yielding the dipyrrole derivative (**19**) as major product (Scheme 2). Similar results were obtained for compounds **14** and **15**. The reaction of **16** and pyrrole in the presence of DCE at higher temperature led to the decomposition of starting material and only polypyrroles were identified as products. Therefore, we performed the reaction at room temperature to obtain monopyrrole and dipyrrole derivatives in 45 % and 21 % yields, respectively.

Notably, treatment of compound **14** with pyrrole in the presence of $BF_3{\cdot}OEt_2$ yielded four compounds: two isomers for each monopyrrole (**20** and **22**) and dipyrrole derivatives (**21** and **23**). This is akin to the situation found in N-confused porphyrins.[11] These isomers have distinct R_f values and were separated via routine column chromatography. NMR

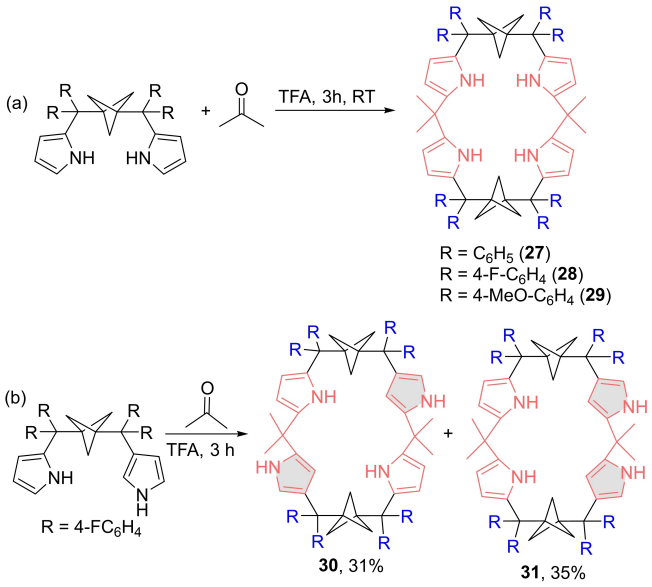


Scheme 2. Synthesis of BCP-pyrrole derivatives **18–26**.

spectroscopic analysis revealed that the first fraction has two pyrrole rings, and both were attached at the α-position, whereas in the second fraction one pyrrole unit has an α-linkage and another pyrrole unit is connected via the β-position. The third fraction has one pyrrole unit connected via the α-position while the fourth fraction contained the pyrrole unit attached via the β-position. Compounds **21** and **23** have distinct NMR spectra but the same molecular ion peak in ESI-MS (*m*/*z* 601.2263 and 601.2269). The ^{1}H NMR spectrum of **21** showed one singlet at 7.41 ppm corresponding to both pyrrolic NHs and three sets of pyrrolic CH signals between 5.97–6.79 ppm. Compound **23** showed five signals corresponding to the six pyrrolic CHs and two singlets for two pyrrolic NHs. A similar NMR profile was reported for N-confused 5,5-dimethyldipyrromethane.[12] Further, we tested different Lewis acids such as TFA, $InCl_3$, and $MgBr_2$ to catalyze the pyrrole-BCP-diol condensation, leading to a significant decrease in the product yield along with the disintegration of BCP moiety.

The first synthesis of calix[4]pyrrole was reported by Baeyer in 1886.[13] Sessler and co-workers discovered the anion detection properties of calix[4]pyrrole in 1996.[14] Since then, calix[4]pyrrole derivatives have been explored as sensors, catalysts, and drug carriers.[8] Taking inspiration from this, we envisioned incorporating the BCP unit into a calixpyrrole-type framework to access a system that was expanded compared to **5**–**7** and where, akin to their use as bioisosteres the "3D" BCP units could give rise to new binding motifs.[15] A reaction of compound **19** with excess acetone in the presence of TFA gave calix[4]pyrrole[2]BCP **27** in a 65 % yield. Compounds **21** and **24** were subjected to similar reaction conditions, yielding calix[4]pyrrole[2]BCP **28** and **29** in 65 % and 71 % yield, respectively. Despite the progress in nonaromatic porphyrinoid chemistry, N-confused analogues are rarely explored, possibly due to their low yields and tedious purification. To this end, we subjected compound **23** to the reaction conditions given in Scheme 3. This reaction gave two isomers, namely **30** and **31** in 31 % and 35 % yield, respectively. Compound **30** exhibits two resonances at 1.64 ppm and 1.57 ppm corresponding to meso-CH_3 groups while HMBC analysis showed a correlation between two CH_3 signals, indicating that both CH_3 groups are connected via a three-bond connection (Figure S43). Furthermore, two methyl groups are connected to two different pyrroles, indicating that this fraction is most likely corresponds to compound **30**. As shown in the NOESY NMR (Figure S44), both NH signals show different types of H–H correlation. The NH resonance at 7.77 ppm shows a correlation with the CH_3 group at 1.63 ppm, whereas NH peak at 7.48 shows a correlation with the CH_3 group at 1.55 ppm and BCP–CH_2 at 1.85 ppm. These correlations indicate that the 1,3-alternate or αβαβ conformation of pyrrole units is prominent in solution.

Compounds **10**–**14**, **16**, **18**, **19**, **21**, and **27** were found to yield diffraction quality single crystals when solutions in $CDCl_3$, CH_3Cl, or CH_2Cl_2 were subjected to slow evaporation. Structural parameter tables and refinement details (Tables S1, S2, and S3) are given in the Supporting Information.[15]



Scheme 3. Synthesis of calix[4]pyrrole[2]BCP derivatives **27**–**31**.

The OH group(s) in compounds **10**–**14** participate ubiquitously in H-bonding as the dominant intermolecular motif. The relative orientation of the bridgehead-appended groups seems to dictate the pattern of non-covalent interactions, with minimal influence of the BCP unit.[16] In compound **10**, the two hydroxyl groups on the BCP scaffold project to the same side of the molecule, forming opposite-facing H-bonding arrangements (Figure S68). Each hydroxyl group in this structure participates in a four-fold hydrogen bonding arrangement as shown in Figure 2 (D···A 2.81–2.87 Å; ∠DHA 160.8°–167.9°); one-dimensional quadruply hydrogen-bonded fibers are formed which propagate on the crystallographic *b*-axis (Figure 2). The presence of four near-identical molecules in the asymmetric unit is indicative of the unusual packing between these fibers, with an offset of $^1/_4$ between adjacent stacks preventing additional transla-

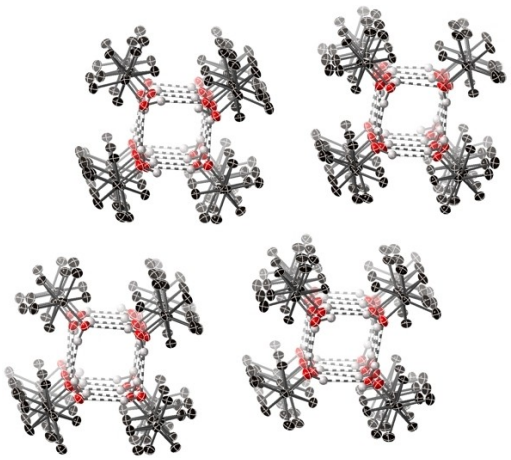


Figure 2. One-dimensional quadruply hydrogen-bonded fibers in **10**.

tional symmetry from being accessed, as observed previously for bicyclo[3.3.1]nonane-diols.[17]

Hydroxyl groups in compound **11** are oriented in an *anti*-arrangement that exhibits intermolecular O–H· · ·O (2.8299 (12) Å; 175.0(17)°) and alkynyl C–H···O (3.2322(14) Å; 164°) interactions to give a two-dimensional network (Figure S69). In compound **12**, the C=O group of $COOCH_3$ moiety and OH group adopt an *anti*-conformation, resulting in the O–H···O interaction at the distance of 2.991(3) Å with an angle of 163(4)° (Figure 3a).

Compound **13**, as shown in Figure 3b, displays a *syn*-arrangement of hydroxy groups. Due to the bulk of the benzhydryl backbone, this hydroxyl group can only access one available hydrogen bond and exhibits disorder of the proton across this bond. This is best described as a 1:1 disorder, with a second orientation of the H atom (H32B and H33B) not participating in H-bonding. The O–H···O distances of 2.994(2) Å (O32) and 2.765(2) Å (O33) indicate that these are on the stronger side of normal O–H···O interactions, not the shorter 'symmetrical' interactions observed for the triethylammonium salt of BCP diacid.[16b]

The crystal structure of **14** clearly shows that both hydroxyl groups participate in two types of intermolecular non-covalent interactions. The F-atom at the *p*-position of the phenylene moiety exhibits O–H···F interaction at a distance of 3.238(2) Å with an angle of 168(2)°. Furthermore, hydroxyl groups contribute to the O–H···O (3.010 (2) Å) bonding with an angle of 167(3)°. The combined intermolecular close contacts in **14** results in a 2D supramolecular polymer (Figure S72). Compound **19** has two pyrrole units in place of the hydroxyl groups of compound **13**. Pyrrolyl and phenyl groups are disordered about the pseudo-threefold axis of the molecule, which is the threefold axis of the trigonal crystal system. This structure is similar to those observed studying symmetry interplay in bis(trityl)alkynes, with this structure resembling the interactions and packing of the Ph_3–C≡C–C≡C–Ph_3 compound.[18] Further X-ray analysis of compound **21** displayed similar packing and disorder characteristics to **19**. Compound **18**, with one hydroxyl and one pyrrole substituent, displays hydrogen bonding similar to **13** and pyrrole/phenyl disorder similar to compound **19**. The pyrrole and phenyl moieties are disordered around the BCP principal threefold axis; the OH group interacts with an equivalent O–H moiety at the distance of 2.991(3) Å with an angle of 163(4)°.

The crystallographically determined structure of macrocycle **27** is shown in Figure 4; this is one of three solvate polymorphs investigated (DCM, chloroform, EtOAc). The macrocycle contains two 1,3-bis(diphenyl(1*H*-pyrrol-2-yl)methyl)bicyclo[1.1.1]pentane units connected via two dimethylmethylene bridges. In the chloroform-solvated compound, BCP units are arranged at approx. 90° to each other and the angle between pyrrole A and B is 87.50° (Figure 4). Only two of the four pyrrolic NH units point inside the macrocycle. Discounting the BCP linkages, the calix[4]pyrrole exhibits the 1,3-alternate orientation (or αβαβ conformation) of pyrrole rings. The conformation of pyrrole and BCP units remained the same under different solvent conditions (Tables S2 and S3); the use of ethyl acetate induced a C–H···O interaction (3.268(14) Å; 147°) between the BCP–CH_2 and C=O subunit of ethyl acetate.

In summary, we present a facile and cost-efficient pathway to incorporate BCP building blocks into functional organic materials.[19] BCP derivatives can be rapidly generated with quaternary carbon atoms at the α-position by this procedure, which is essential for pushing medicinal chemistry beyond the aryl plateau. Crystallographic studies of the BCP structures indicate superficial similarity to structures with alkynyl linkers and show characteristic interactions arising from the strained CH_2 units. Furthermore, for the first time, the incorporation of a rigid scaffold in a porphyrin analogue was achieved, a crucial milestone in understanding the interactions of these carbon motifs with

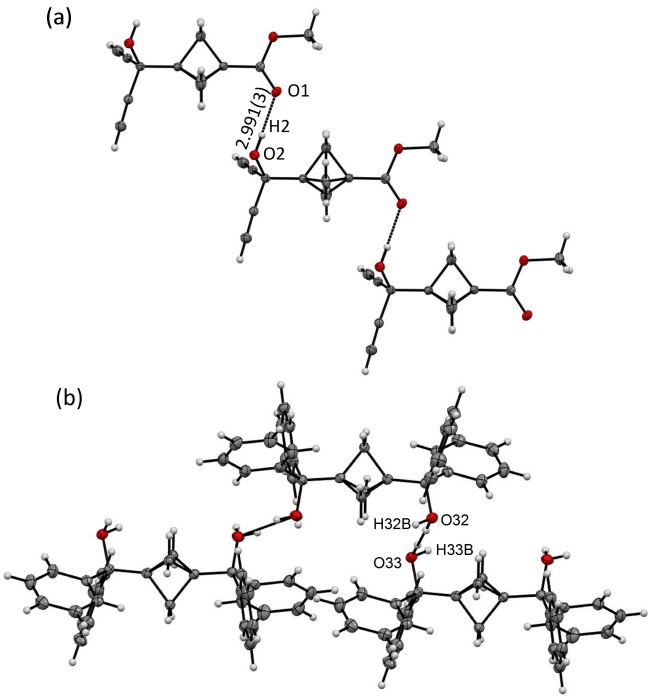


Figure 3. H-bonding pattern in: a) compound **12**; b) compound **13**.

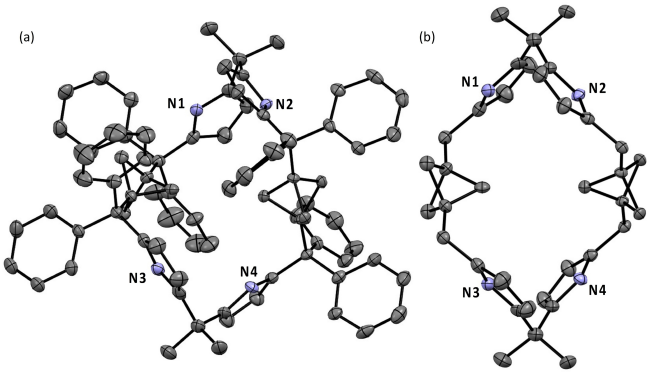


Figure 4. Molecular structure of: a) **27**; b) **27** with phenyl groups and hydrogen atoms omitted for clarity.

partners localized in the macrocycle core. We are currently exploring the use of these calix[4]pyrrole-type and other BCP-infused systems as molecular receptors with orthogonal selectivity, where supramolecular interaction can lead to a further understanding of these cryptic moieties.

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Conflict of Interest

The authors declare no conflict of interest.

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