Communications

Novel Protecting Strategy for the Synthesis of Porphyrins with Different Distal and Proximal Superstructures

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Received September 9, 1998

The four distinct atropisomers of tetrakis-5,10,15,20-(*o*-aminophenyl)porphyrin (TAPP) **1a**−**d** (Scheme 1),[1] readily available from the reduction of the corresponding nitro compounds, provide four very different precursors for the synthesis of superstructured porphyrins. A great number of syntheses of porphyrin-based catalysts and functionalized porphyrins modeling enzymatic activities have hinged on the derivatization of one of the four atropisomers of TAPP, the symmetric αααα- and αβαβ-TAPP being the most popular.[2] However, porphyrins with different distal and proximal superstructures, which resemble the metalloporphyrin sites in biological systems much better, are hard to obtain due to the lack of discrimination of the amino groups.

Work in our group and elsewhere involving the preparations of "tailed" porphyrins employ the unique shape of the ααα*β* atropisomer **1b**. However, the syntheses usually start with αααα-TAPP **1a**, which circumvents the α versus *β* issue but adds a late, low-yield rotation step.[3−5] Our desire for a generally applicable and more straightforward route led to the development of an extremely useful ααα*β*-TAPP analogue with a protected *β* picket, allowing selective, high-yield derivatizations of the three α amines. This communication describes a method for the synthesis/enrichment of **2**, which we call *β*-trityl ααα*β*-TAPP (3.1Tr-TAPP), and first examples of its versatility as a preorganized synthon in the syntheses of heme model ligands.

To obtain **2**, TAPP (mixture of all four atropisomers) is first reacted with 1 equiv of triphenylmethyl bromide, yielding a statistical mixture of all possible atropisomeric un-, mono-, and bistritylated TAPP's. This mixture is then absorbed on basic alumina and heated in toluene/heptane for 15 h. In this process, 3.1-TrTAPP **2** and αααα-TAPP **1a** are selectively enriched and can be conveniently isolated by flash chromatography in 30% (**2**) and 26% (**1a**) yield, respectively (Scheme 1). The procedure resembles Lindsey's enrichment method for αααα-TAPP in that the most polar atropisomer builds up to the largest extent.[6,7]

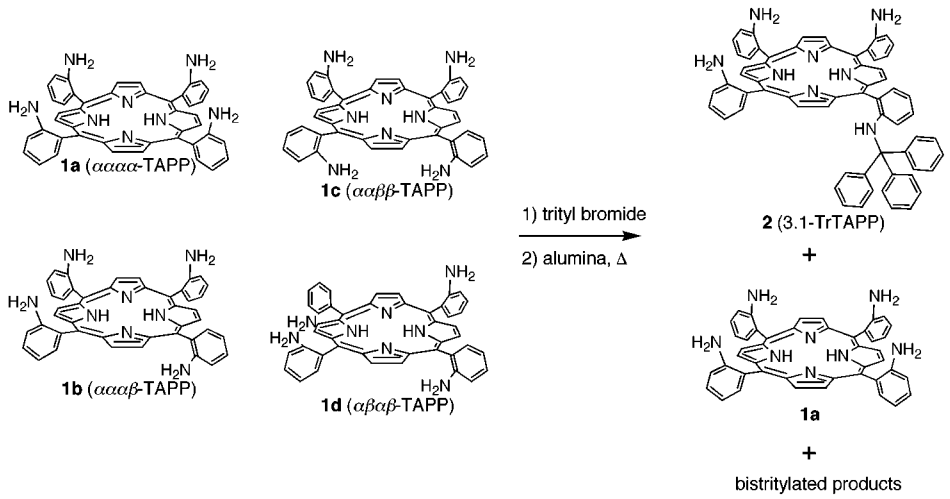
To ensure the structural assignment beyond the NMR analysis, **2** was transformed into the known ααα-tris(*o*-pivaloylamido)phenyl-*β*-(*o*-aminophenyl)porphyrin[3] by treatment with pivaloyl chloride, followed by acidic removal of the protection group. The NMR spectra and R_f value of the material thus obtained were identical with those of an authentic sample.

The availability of 3.1-TrTAPP **2** opens up unique possibilities for the rational design of heme models. This can best be shown by the syntheses of the new cytochrome *c* oxidase model ligands **3** and **4** (Scheme 2). Starting with **2**, acylation of the three α pickets with chloroacetyl chloride[8] or acryloyl chloride[9] yields the porphyrins **5** and **6**, respectively, both carrying activated pickets exclusively on the distal face. Simple acid treatment (HCl gas, dichloromethane, 10 min) quantitatively removes the trityl group to give **7** and **8**, respectively. No interference with the reactive chloro- and acryloyl pickets was noticed. The reactions of the aminoporphyrins **7** and **8** with pyridyl acid chlorides (prepared in situ from the respective acids **11** and **12**) produce **9** and **10** and thus finish the construction of the proximal sites. **10** undergoes a 3-fold Michael addition reaction with triazacyclononane (TACN) to give **4** under conditions similar to those described by us earlier.[9]

The introduction of the biologically more relevant imidazole ligands can best be achieved from **9** and the protected imidazole **13** via a substitution/elimination sequence.[10] Nonprotected imidazoles predominantly quarternize during this reaction, bridging two pickets and yielding only trace amounts of the desired cytochrome *c* oxidase model ligand **3**.

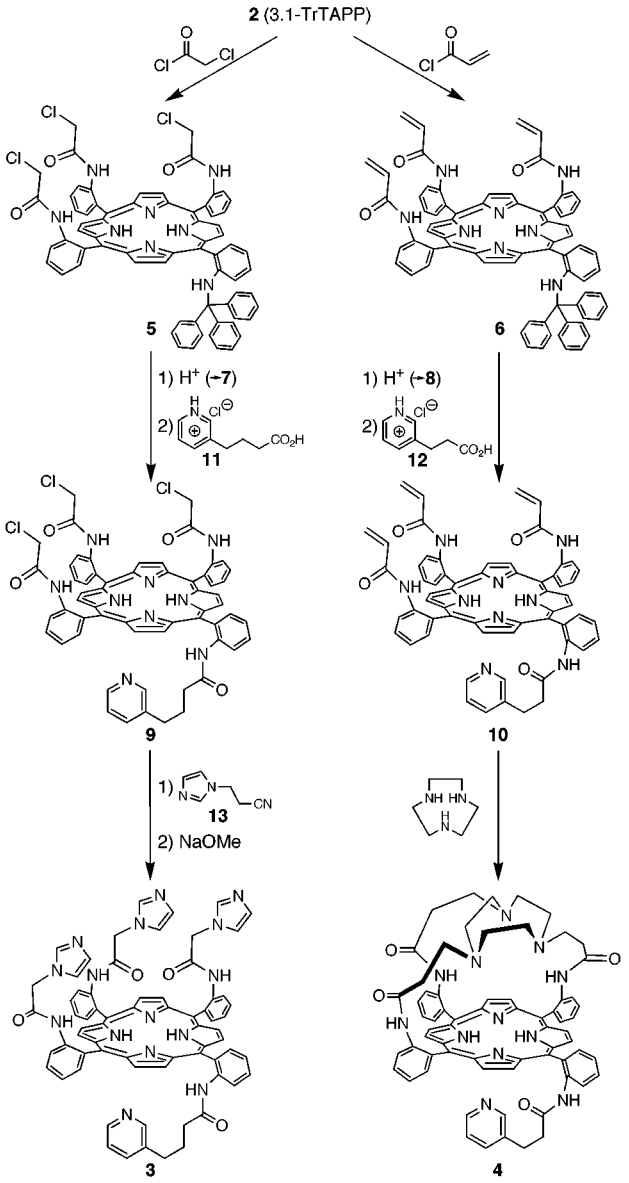
Applying the above reactions to **5** and **6**, respectively, the distal superstructures can also be completed first (Scheme 3). Under the chosen reaction conditions, this results in **14** and **15**, with thermally induced detritylation occurring only

Scheme 1



10.1021/jo981834r CCC: $15.00
Published on Web 10/27/1998

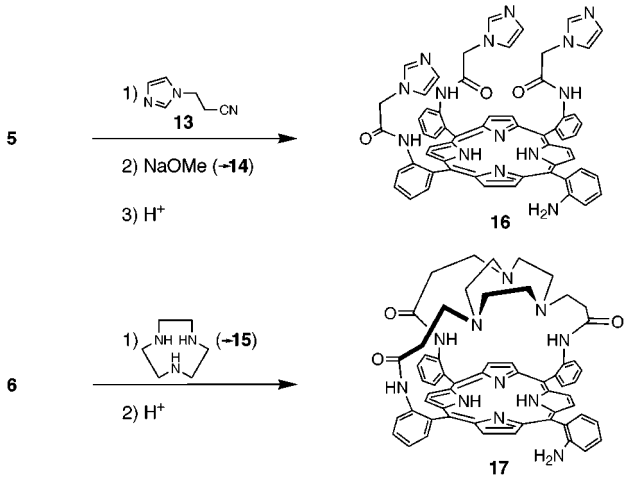
Scheme 2



to a negligible extent. Treating **14** and **15** with acids cleanly releases the aminoporphyrins **16** and **17**, respectively, which can then be further derivatized.

As demonstrated, the use of 3.1-TrTAPP **2** as a valuable key intermediate permits the highly selective and flexible construction of the distal and the proximal face of nonsymmetrical porphyrins. Within this methodology, the building blocks "axial ligand" and "superstructure" become modular and thus easy to exchange. It can be foreseen that this general approach will find broad application in the design and synthesis of a large number of customized porphyrins.

Scheme 3



Acknowledgment. We thank the NIH (Grant 1R01 GM-17880-28) and the NSF (Grant CHE 9612725) for financial support. We also thank the Mass Spectrometry Facility, University of California, San Francisco, supported by the NIH (Grants RR 04112 and RR 01614).

Supporting Information Available: Experimental procedures and characterization data for compounds **2**–**10**, **14**–**17** (15 pages).

JO981834R

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