Supplemental Information

Figure SI 1. Mass spectrum of Hb-cyclooctyne (β-subunits cross-linked). ((β-subunit (15867.22-1.01) × 2) + C_{26}O_{7}N_{2}H_{30}(482.58)) = 32215.00 g/mol. We cannot attribute the mass spectrum heterogeneity to an impurity of the cyclooctyne handle, since Hb-cyclooctyne reacts to completion in the presence of bis-azide (see Figure SI 3). The complex spectrum may result from transformations occurring during mass analysis.

Figure SI 2. Mass spectrum of Hb-azide (β-subunits cross-linked). (β-subunits ((15867.22-1.01) × 2) + C_{17}O_{3}N_{4}H_{12}(320.33)) = 32052.75 g/mol.
Figure SI 3. Mass spectrum of Hb-cyclooctyne (β-subunits cross-linked) modified with bis-azide (4,4’-diazidediphenylsulfone) only. ((β-subunit (15867.22-1.01) × 2) + C_{26}O_{2}N_{2}H_{30} (482.58) + C_{12}SO_{2}N_{6}H_{8} (300.30)) = 32515.00 g/mol.

Figure SI 4. Reverse-phase HPLC of Hb-alkyne under dissociating conditions. Peaks are as follows: heme (10 min.); α-subunits (40 min.); β cross-linked subunits (alkyne modified, 54 min.).
**Figure SI 5.** Mass spectrum of Hb-alkyne (β-subunits cross-linked). \(((β\text{-subunits} \times 2) + C_{20}O_7\text{NH}_{23}(389.44)) = 32121.86 \text{ g/mol.}\)

**Figure SI 6.** Size-exclusion HPLC trace of the purified bis-tetramer.
Figure SI 7. Size-exclusion HPLC trace of the products of the reaction of Hb-azide with Hb-cyclooctyne after 18 days.

Figure SI 8. Size-exclusion HPLC trace of the products of the reaction of Hb-cyclooctyne with bis-azide (PEG spacer).