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[9] The equilibrium constants at 298 K were determined by integrating the ^{1}H NMR spectrum (500 MHz, D_2O) of the mixture containing 5.0 mM $K_{12}[Ga_4L_6]$ and 5.0 mM guest in an NMR tube. The ^{1}H NMR spectra were measured both 30 min and 2 days after the initial mixing. No change was observed in the spectra over time, implying that equilibrium was achieved within 30 min of mixing.

[10] Crystal data for $K_5[Et_4N]_7[Fe_4L_6]\cdot 8H_2O\cdot 3CH_3OH$ were collected with a Siemens SMART diffractometer equipped with a CCD area detector;[12] crystal size $0.25\times 0.23\times 0.10$ mm; $T=-120\,^\circ$C, $\lambda Mo_{K\alpha}=0.71073$ Å; point group $I\bar{4}3d$ (No. 220), $a=43.706(8)$ Å, $V=83488$ Å^3, $Z=16$, $\mu=0.45$ mm^{-1}, F(000) = 35808, $\rho_{calcd}=1.333$ Mg m^{-3}, $2\theta_{max}=41.67^\circ$. Of the 136092 reflections collected 7336 were unique ($R_{int}=0.214$). The structure was solved by direct methods and was refined on F^2 using SHELXTL.[13] Data were corrected for Lorentz and polarization effects. An empirical absorption correction was applied using XPREP[13] (ellipsoidal model, $R_{int}=0.036$, $T_{max}=0.895$, $T_{min}=0.834$). The iron atoms, oxygen and nitrogen atoms of the ligands, the half-occupancy potassium, and the nitrogen and carbon atoms of the full occupancy Et_4N^+ counterion were refined anisotropically. Hydrogen atoms were included as riding on their respective carbon and nitrogen atoms for all but the disordered counterions and solvent molecules. Not all carbon atoms were found for the disordered Et_4N^+ counterions. The N–C and C–C distances for these disordered ions were set to target values of 1.4 and 1.5 Å. An antibumping restraint was applied to carbon atoms of the disordered Et_4N^+ on the interior of the tetrahedral cluster. Weighting scheme: $1/[\sigma^2F_o^2+(0.1660p)^2+779.981p]$, where $p=((F_o^2,0)_{max}+2F_c^2)/3$. Final $R_1=0.0978$ for 4672 reflections with $F_o>4\sigma(F_o)$; 4672 Friedel unique data, 542 parameters, 14 restraints, $3.75^\circ<2\theta<34.58^\circ$); for all 7336 data, $wR_2=0.3288$, GOF = 1.205; max/min residual density $+0.62/-0.32$ e Å^{-3}, Flack parameter = 0.03(5).[14] Crystallographic data (excluding structure factors) for the structure reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-100947. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: (+44) 1223-336033; e-mail: deposit@ccdc.cam.ac.uk).

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A Novel Chromophore Selectively Modifies the Spectral Properties of One of the Two Stable States of the Plant Photoreceptor Phytochrome**

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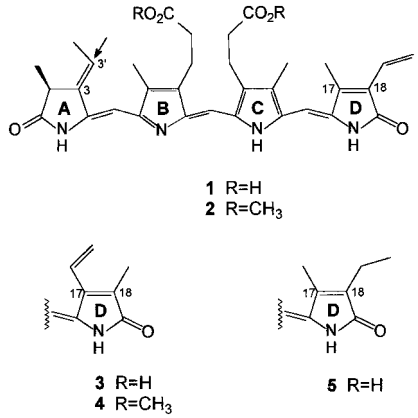
Phytochromes are plant photoreceptors that consist of a protein (125–140 kDa) covalently bound to the open-chain tetrapyrrole chromophore phytochromobilin (**1**, Scheme 1).



Scheme 1. Structural formulas of the native phytochrome chromophore phytochromobilin (**1**), the isomer "iso"-phytochromobilin (**3**, described here for the first time), the corresponding methyl esters **2** and **4**, and phycocyanobilin (**5**). The arrow marks the 3′ position on ring A of **1**, which is covalently attached to the apoprotein through nucleophilic attack by a cystein thiol group. The B/C tautomeric form shown here was selected in analogy to the crystal structure of a 2,3-dihydrobilatriene abc model compound.[20]

Initiated by $Z\rightleftharpoons E$ photoisomerization of a double bond of **1**,[1] the phytochrome undergoes a multistep rearrangement steered by subtle chromophore–protein interactions. This ultimately leads to a biological signal transduction and control of a wide array of physiological processes as a function of wavelength and intensity of the absorbed light.[2] Accordingly, effects on absorption and photochemical properties upon selective modifications of the protein and chromophore components may significantly contribute to the understanding of the light-induced phytochrome transformations.

The synthesis of native and mutated forms of the phytochrome apoprotein (i.e., chromophore-free protein) has been accomplished previously,[3] as has the assembly of the apoproteins with native **1** and with phycocyanobilin (**5**).[1c, 3] However, the amount of **1** isolable from algae[4] has been

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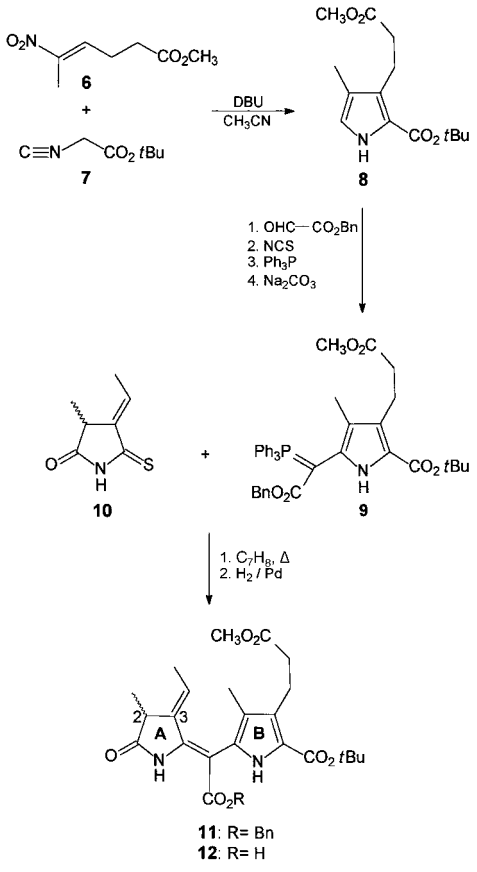
insufficient for detailed spectroscopic investigations. More efficient and variable syntheses of **1**[5] and of modified tetrapyrrole chromophores (including substitutional isomers and isotopomers[7]) are therefore urgently needed.

We now report new syntheses of **1** and a substitutional isomer, "iso"-phytochromobilin (**3**, Scheme 1), based in part on previous work. Whereas Gossauer and collaborators[8] synthesized only the dimethyl esters of several open-chain tetrapyrroles, we present here the very labile free acids **1** and **3**, and document the ability of these compounds to form functional chromoproteins with heterologously produced phytochrome apoprotein.

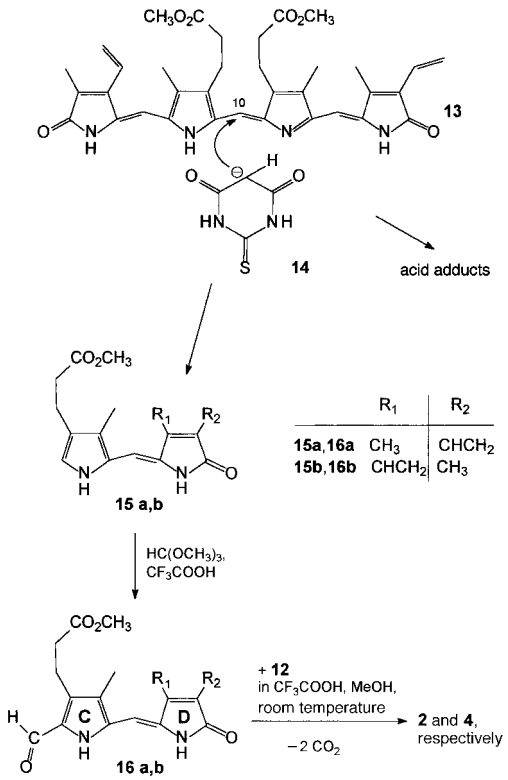
Racemic thiosuccinimide **10** (ring A) was prepared by a known route.[8b] The conditions for the subsequent thio-Wittig reaction must be chosen such that the 3-ethylidene structure, which is essential for covalent binding to the protein,[9] does not rearrange to the more stable 2,3-dehydro structure with an unsaturated ring A. In contrast to the earlier synthesis, ring B was prepared by cyclization[10] of nitroolefin **6**[11] with isocyanide **7**[12] to form **8** (Scheme 2), rather than by a Paal–Knorr condensation. Substitution of the free α position of **8**



Scheme 2. Synthesis of phosphorus ylid **9** (ring B) and coupling with separately prepared **10** (ring A)[8b] to give dipyrromethenone **11**. Bn = benzyl, *t*Bu = *tert*-butyl, NCS = *N*-chlorosuccinimide, DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene.

with a benyloxycarbonyl(hydroxy)methyl group was followed by chlorination and reaction with triphenylphosphane to provide ylid **9**,[13] which was combined with **10** in a thio-Wittig reaction to afford **11**. Hydrogenolysis of the benzyl ester group of **11** gave dipyrromethenone **12**. All products gave the expected elemental analyses. Since rings B and C in **1** are identical, and since several syntheses are known for ring D,[14] the present choice of a stepwise construction of the ring system allows for a broad variation in the substitution pattern and for the introduction of stable isotope labels. The latter are of decisive importance for the interpretation of the complex vibrational spectra of the chromophore in phytochrome.[3g]

Instead of a stepwise assembly by annelation of rings C and D, we chose the more efficient cleavage at C10 of biliverdin IXα dimethyl ester (**13**) with the thiobarbiturate anion (**14**).[15] This alternative affords the two rings already joined in the form of the dipyrromethenones **15a** and **15b** (Scheme 3).



Scheme 3. Cleavage of biliverdin IXα dimethyl ester **13** by thiobarbiturate anion (**14**). The reaction affords both a dipyrromethenone with rings A–B (**15b**) and a thiobarbiturate adduct of rings C–D (not shown) as well as to dipyrromethenone C–D (**15a**) and the corresponding adduct with rings A–B (not shown).

After chromatographic separation (silica gel, chloroform/ethyl acetate 1/1) the two products were formylated separately to **16a** and **16b**, which were used for the construction of **1** and **3**. The two halves, **12** and **16a** or **16b**, were coupled[6] to the corresponding dimethyl esters **2** and **4**, respectively, in about 40% yield (see Table 1). The structural assignment of **4** is based on ^{1}H NMR spectra of the two esters, in which the ABX and AMX signal groups unequivocally establish C17 (**4**) and C18 (**2**) to be the positions of the vinyl substituents.[16] Synthesis of the acids **1** and **3** from the corresponding esters proved difficult because of the instability of the products; it was achieved only by hydrolysis on an acidified ion-exchange resin (Dowex-50WX8-200, 40% trifluoroacetic acid, 48 h, room temperature, chromatographic purification, and crys-

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Table 1. Physical and spectroscopic data for **3**, **4**, and **16b**.

3: ^{1}H NMR (400 MHz, [D$_5$]pyridine): $\delta = 1.50$ (d, 3H, $J = 7.51$ Hz), 1.69 (d, 3H, $J = 7.26$ Hz), 2.02, 2.10, 2.16 (3s, each 1H), 2.85 (m, 4H), 3.10 (t, 2H, $J = 7.23$ Hz), 3.18 (t, 2H, $J = 7.35$ Hz), 3.32 (q, 1H, $J = 8.20$ Hz), 5.59–5.76 (AB, 2H, partially overlapped by the H_2O peak), 5.87 (s, 1H), 6.26 (s, 1H), 6.32 (q, 1H, $J = 7.31$ Hz), 6.87 (m, X), 7.35 (s, 1H)

4: M.p. 208 °C; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 1.30$ (d, 3H, $J = 7.54$ Hz), 1.84 (d, 3H, $J = 6.73$ Hz), 1.88, 2.00, 2.08 (3s, each 3H), 2.52 (t, 2H, $J =$ 7.80 Hz), 2.53 (t, 2H, $J = 7.55$ Hz), 2.87 (t, 2H, $J = 7.82$ Hz), 2.91 (t, 2H, $J =$ 7.53 Hz), 3.09 (q, 1H, $J = 7.38$ Hz), 3.65, 3.66 (s, each 3H), 5.62 + 5.64 (AB, $J_{AB} = 1.61$, $J_{AX} = 17.86$, $J_{BX} = 11.51$ Hz), 5.76 (s, 1H), 6.09 (s, 1H), 6.33 (q, 1H, $J = 7.35$ Hz), 6.59 (s, 1H), 6.59–6.70 (X, 1H); UV/Vis (MeOH, 0.5% NEt_3): λ_{max} (ε) = 366 (42000), 617 nm (16100); FT-IR (CCl_4): $\tilde{\nu} = 3435$, 3343, 2987–2915, 1742, 1733, 1698, 1666, 1619, 1590, 1436, 1252, 1165, 986, 954, 917 cm^{-1}; FAB-MS: m/z (%) = 613 (18)[M^+], 586 (7), 502 (19), 467 (19), 418 (14), 391 (12), 348 (39), 334 (100); HR-FAB-MS ($C_{35}H_{41}N_4O_6$): calcd 613.3026, found 613.3034

16b: M.p. 235–237 °C; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 2.09$, 2.11 (2s, each 3H), 2.58 (t, 2H, $J = 7.65$ Hz), 3.06 (t, 2H, $J = 7.64$ Hz), 3.65 (s, 3H), 5.65 + 5.68 (AB, 2H, $J_{AB} = 1.60$, $J_{AX} = 20.20$, $J_{BX} = 13.83$ Hz), 6.10 (s, 1H), 6.59–6.66 (X, 1H), 9.75 (s, 1H), 10.55 (brs, 1H), 10.75 (brs, 1H); UV/Vis (MeOH): λ_{max} (ε) = 405 (24250), 271 (11500), 243 nm (11800); FT-IR (KBr): $\tilde{\nu} = 3335$, 2949–2858, 1734, 1675, 1559, 1443, 1340, 1302, 1250, 1173, 1057, 993, 761 cm^{-1}; EI-MS: m/z (%) = 328 (100)[M^+], 313 (7), 299 (18), 269 (15), 241 (19), 225 (20), 197 (5), 183 (4), 134 (5), 120 (4), 106 (3); HR-MS ($C_{18}H_{20}N_2O_4$): calcd 328.1423, found 328.1421

tallization from chloroform/1% methanol/*n*-hexane). In view of their instability, the free acids were used in the assembly experiments (see below) immediately after their ^{1}H NMR spectra were recorded. The syntheses described offer the first approach to acids **1** and **3** and related compounds in quantities sufficient for spectroscopic investigation after incorporation into protein. However, the overall yield is still relatively modest.

Acids **1** and **3** were incubated with recombinant oat apophytochrome[17] under standard conditions in order to test, in the case of **1**, the reproducibility of the phytochrome absorption values for the native chromoprotein (λ_{max} = 667 nm for P_r and 730 nm for P_{fr})[18] and, in the case of **3**, to search for any effect of the modified substitution pattern of ring D on the spectral properties. The maxima in the difference spectrum (Figure 1) for chromoprotein constructed with **1** ($\lambda_{max} = 665$ nm for P_r and 728 nm for P_{fr}) are in accord with values obtained for native phytochrome extracted from etiolated oat. Based on our experience,[3d] the hypsochromic shift by a few nanometers may result from a slightly altered conformation of the apoprotein owing to the heterologous expression in yeast.[19] Recombinant apophytochrome can also be assembled with phycocyanobilin (**5**) obtained by extraction of algae. Tetrapyrrole **5** differs from the native chromophore **1** only with regard to saturation of the vinyl substituent on ring D (18-ethyl instead of 18-vinyl; Scheme 1); because of the shortened π-electron system, both maxima in the chromoprotein are shifted hypsochromically by about 14 nm ($\lambda_{max} = 653$ nm for P_r and 717 nm for P_{fr}; see also curve "PCB" in Figure 1; for the absorption maxima for the various phytochromes, see Table 2).

The P_r form of chromoprotein assembled with the "iso"-phytochromobilin **3** displays an absorption maximum practically identical to that of the native chromophore **1** (λ_{max} = 663 nm). In contrast, in the P_{fr} form, and also in the

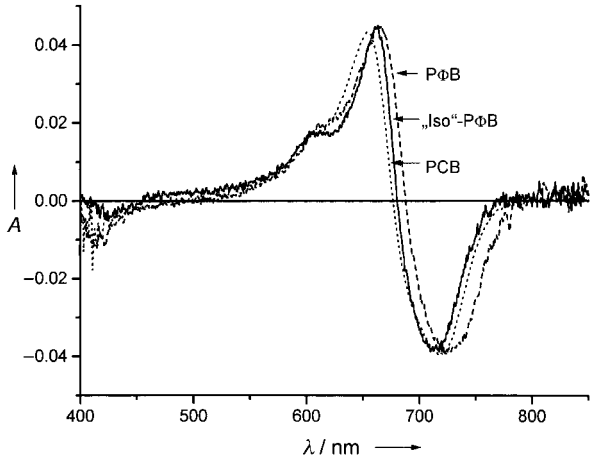

Figure 1. $P_r - P_{fr}$ Difference spectra of the recombinant phytochromes obtained by assembly of the heterologously expressed apoprotein with phytochromobilin (**1**; PΦB) and with "iso"-phytochromobilin (**3**; "iso"-PΦB). The difference spectrum for recombinant phytochrome assembled with phycocyanobilin (**5**, PCB)[17] is also shown. The absorption values on the ordinate refer to the spectra of the chromoproteins obtained by assembly with **1** and **3**. The amplitude of the shorter wavelength maximum of **5** was normalized to that of **1**.

Table 2. Absorption maxima for native and recombinant phytochromes.

Phytochrome type	Chromophore	λ_{max} [nm]; P_r, P_{fr}
native phytochrome[a]	**1**	667, 730
recombinant phytochrome	**1**[b, c]	665, 728
recombinant phytochrome	**3**[b]	663, 714
recombinant phytochrome	**5**[c]	653, 717

[a] Prepared from yeast. [b] Synthetically prepared compound. [c] From material extracted from algae.

chromoprotein assembled with phycocyanobilin **5**, absorption is shifted hypsochromically to 714 nm.[17]

The positions of the absorption maxima indicate that the protein surface of the chromophore pocket tolerates the

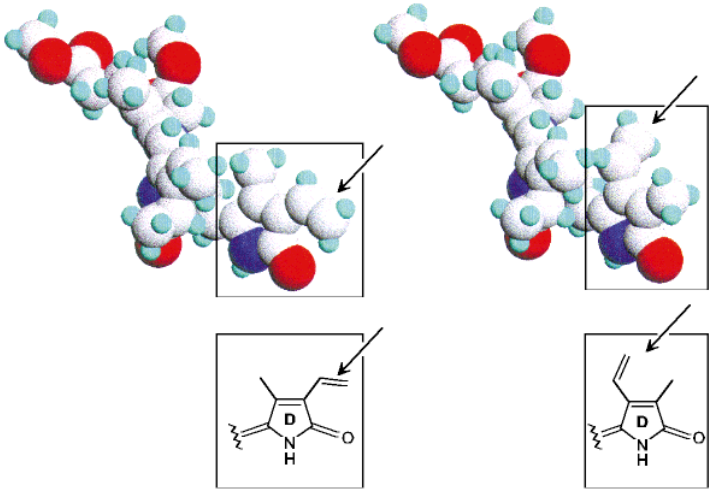

Figure 2. Structures of the *Z,Z,E* configured compounds **1** and **3** optimized at the PM3/MM$^+$ level (Hyperchem, version 4.0). Note that the differing conformations in ring D were generated without regard to interactions with the protein pocket of the phytochrome. Arrows indicate the positions of the vinyl substituents.

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altered substitution on ring D of **3** in the P_r form, whereas in the P_{fr} form the chromophore–protein interactions discriminate between the substitution patterns of **1** and **3**. There remains the question of whether this selectivity of the chromophore–protein interactions reflects either steric and/or electronic effects (see Figure 2).

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[18] P_r and P_{fr} represent the thermally stable forms in the phytochrome photocycle, which absorb red (r) and far-red (fr) light, respectively.

[19] Correspondingly shifted absorption values are also found when phytochrome is reconstituted from recombinant oat apoprotein with native phytochromobilin (**1**), which is isolable from algae in small amounts and only with difficulties. This successful reproduction of phytochrome reconstitution based on native **1** minimizes the risk of artifacts that might have arisen in reconstitution employing the now readily available synthetic **1**.

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Tweezers with Different Bite: Increasing the Affinity of Synthetic Receptors by Varying the Hinge Part**

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Despite the tremendous progress in the design and synthesis of receptor molecules with predicted binding properties, it remains a difficult task to design a molecule capable of binding to a particular ligand. Therefore, recent efforts have turned to the more "biomimetic approach" of combinatorial chemistry for the generation of libraries of synthetic receptors capable of binding certain desired ligands. The approach is inspired by nature's very own combinatorial approach so clearly demonstrated by the immune system.

Based on the successful concept of "tweezerlike" two armed synthetic receptors,[1] we have developed synthetic receptors consisting of peptidosulfonamide peptidomimetics.[2] We would like to prepare libraries of tweezerlike receptors that can be screened for their binding affinity to a variety of ligands, peptides, other biomolecules (for example, those that are present on pathogenic organisms), drugs, and signaling molecules. Although our present synthetic receptor showed a remarkable binding selectivity,[2] to have further possible applications its binding affinity with ligands had to be increased. We now describe the results of incorporating less flexible "hinges" in tweezerlike synthetic receptors.

Our present "tweezerlike" synthetic receptors consist of three different parts (Scheme 1): A hinge to which the tweezer arms are attached; a dye or a solid-phase bead attached to this hinge; and two binding arms, which at present consist of peptidosulfonamide peptidomimetics. Based on the original hinge in tweezer **1**, hinges in tweezers **2**–**6** were selected to gradually vary the flexibility and interchain distance, or both, between the amino nitrogen atoms.

The route for the preparation of the tweezerlike synthetic receptors is exemplified by the preparation of tweezers **2** and **5** in Schemes 2 and 3. The bis(aminomethyl)benzoic acid hinge present in receptor **2** was synthesized from 3,5-dimethylbenzoic acid (**7**).[3] We took advantage from the fact

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