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Stereoselective Synthesis of Concave Spacers for Long-Range Electron Transfer Models

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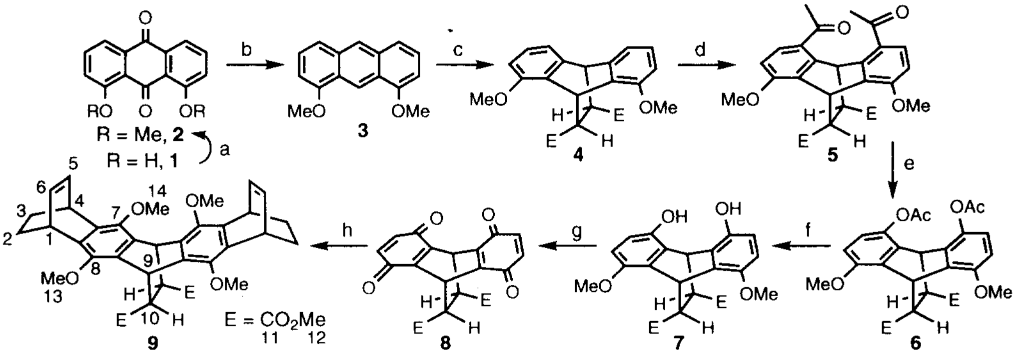
Abstract: Syntheses of concave spacers (**9**, **27**) proceeded via stereoselective Diels-Alder reactions. Successful preparation of asymmetrical spacer **27** relied on regioselective protection of mutual precursor **7**. Copyright © 1996 Elsevier Science Ltd

Investigations of biologically important long-range (≥ 10 Å) electronic processes (e.g., electron transfer, energy transfer, and paramagnetic electron spin exchange) have focused on the controversial role of the intervening medium between electronically coupled species.[2-4] Fundamental insights can be achieved experimentally by controlling the parameters that affect electronic coupling, including distance, orientation, and intervening medium.[5,6] To develop controllable systems that facilitate studies of intervening media, electron donor–spacer–acceptor structures were designed to be rotationally locked to control the orientation and distance parameters and to be concave to allow one to readily change the intervening medium in the concave space between the coupled donor and acceptor (ca. 10 Å apart). The syntheses[7] of symmetrical and asymmetrical, concave molecular spacers (discussed below) employed current methods of regio- and stereochemical control.

A C_2 symmetrical, concave spacer **9** was obtained via a series of Diels-Alder additions to anthracene **3** (Scheme 1);[8] however, precursor **8** was prone to retro Diels-Alder decomposition, especially above 25 °C. From 100 mg of precursor **7**, diquinone **8** was consistently obtained in ca. 70% yield; however, larger scale reactions gave poor yields (< 25%) accompanied by retro Diels-Alder products. To deter such decomposition,

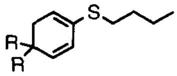


Scheme 1

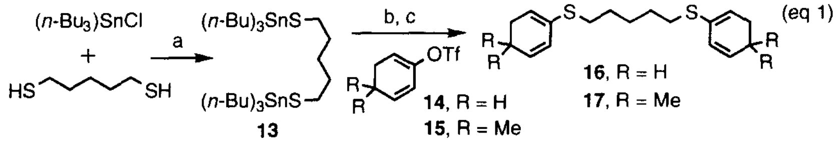
Conditions: (**a**) NaH (3.2 eq), Me_2SO_4 (3.8 eq) THF, reflux, 36 h. (**b**) (i) $NaBH_4$ (4.4 eq) MeOH, 0 °C → 25 °C, 1 h, repeat; (ii) Na (6 eq), NH_3, THF, EtOH (8:3:1), –78 °C, 1 h; (iii) DDQ (1.1 eq), toluene, reflux, 12 h. (**c**) dimethylfumarate (2 eq), Et_2AlCl (4 eq), toluene, 0 °C, 4 h. (**d**) (i) AcCl (4.2 eq), AgOTf (3.7 eq), CH_2Cl_2, –50 °C, 10 min; (ii) add'n of **4**, –40 °C, 4 h. (**e**) MCPBA (3 eq), Na_2HPO_4 (6 eq), CH_2Cl_2, reflux, 12 h. (**f**) MeOH, conc. HCl (0.5 eq), reflux, 1 h. (**g**) CAN (5 eq), CH_3CN, H_2O (3:1), 0 °C, 30 min. (**h**) (i) 1,3-cyclohexadiene (2.2 eq), Me_2AlCl (0.1 eq), CH_2Cl_2, 0 °C, 30 min; (ii) NaH (4.4 eq), Me_2SO_4 (4.6 eq), THF, reflux, 2 h.
Yields: **2** (77%), **3** (90%), **4** (91%), **5** (ca. 70%), **6** (ca. 90%; 60% from **4**), **7** (100%), **8** (71%), **9** (72%).

the bridge ester groups of adduct **4** can be reduced with LAH (1.4 eq, −78 °C, 8 h; 88% diol). Despite its instability, diquinone **8** served as a dienophile for double addition of 1,3-cyclohexadiene to produce spacer **9** (72%) isolated as a single diastereomer with C_2 symmetry (by ^{1}H and ^{13}C NMR analysis).[9] The exact structure of **9** was determined by X-ray diffraction[10] and found to be as illustrated with the bridge olefins *anti* to the central bicyclic bridge. The diastereomeric selectivity can be attributed to *endo* Diels-Alder additions to the least hindered faces of diquinone **8**. In the crystal structure of **9**, the distance between the centers of the bridge olefins is 10.1 Å, whereas the shortest distance through the bonds of **9** is 14.66 Å.

To prepare a concave spacer with asymmetric ends, the sequential addition of two different dienes to diquinone **8** was attempted; however, the initially introduced diene (1,3-cyclohexadiene, 1 mol equiv) produced symmetrical spacer **9** in 43% yield, much higher than for a statistical distribution of products (25% expected). An alternative approach employed tethered dienes to promote regio- and stereochemical control; this approach was tested with bis(1,5-cyclohexadien-1-yl)1,5-pentanedisulfide **16**.[11] Rather than producing Diels-Alder adducts, the tethered dienes were aromatized by *p*-benzoquinone and by diquinone **8** via hydrogen transfer. In contrast, the analogous nontethered diene **11** gave Diels-Alder adducts of *p*-benzoquinone (58% yield) under identical conditions (refluxing benzene, 10 mol% BHT). Cyclohexadienes **12** and **17** with *gem*-dimethyl substituents to block aromatization did not undergo Diels-Alder addition to *p*-benzoquinone.



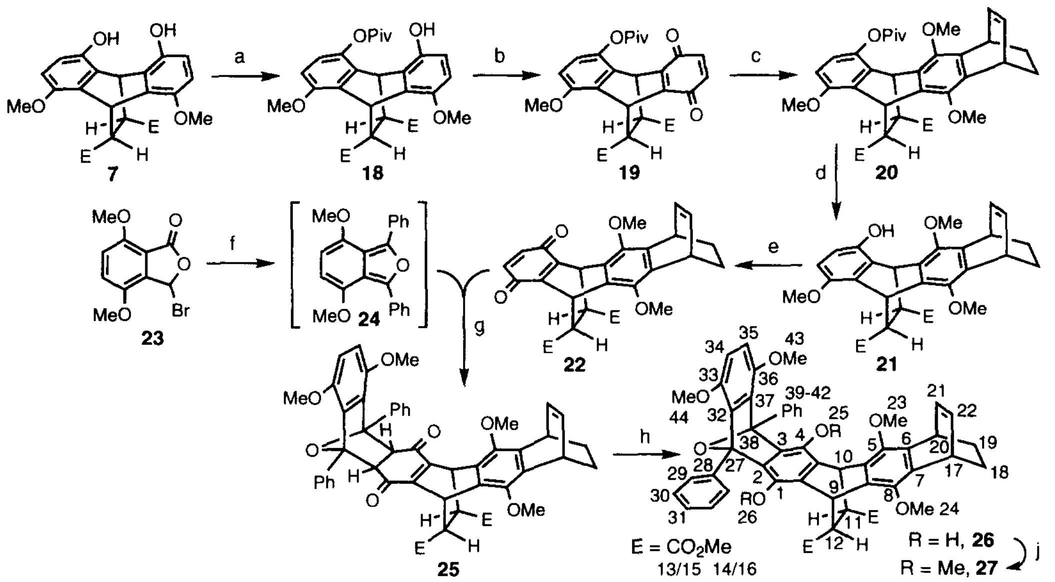
11, R = H
12, R = Me



Conditions: (**a**) *t*-BuOK (2.5 eq), 25 °C, 4 h. (**b**) Prep'n of **14**: (i) 2-cyclohexen-1-one, LDA (1.1 eq), −78 °C, 2 h; (ii) PhN(Tf)$_2$ (1.1 eq), 0 °C, 16 h. (**c**) **14** (2 eq), Pd(Ph$_3$)$_4$ (10 mol%), LiCl (15 eq), THF, reflux, 4 h.
Yields: **13** (93%), **14** (88%), **15** (82%), **16** (89%), **17** (69%).

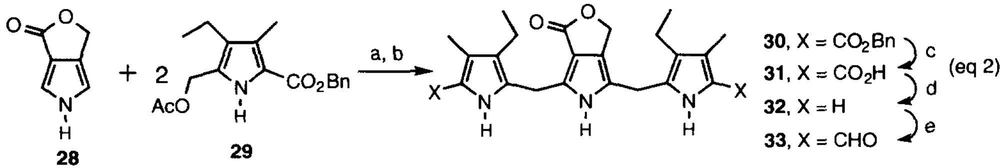
The successful preparation of an asymmetrical spacer relied on regioselective monoprotection of diphenol **7** (Scheme 2). The sterically more accessible phenol of **7** (proximal to a bridge hydrogen) was selectively protected by pivaloyl chloride.[12] Oxidation of the remaining phenol **18** by $NaIO_4$ gave quinone **19** in higher yield (73%) than oxidation by cerium(IV) ammonium nitrate (CAN) (37%; cf. **8**).[13] The first diene was added to quinone **19**. Subsequent deprotection of the pivaloylated phenol, oxidation to quinone **22**, and addition of the second diene **24** completed the construction of spacer **27**. As the original target was a porphyrin-concave spacer-quinone structure, a bridgehead hydroquinone (quinone precursor) was incorporated in spacer **27** via Diels-Alder addition of isobenzofuran **24**.[14,15] A key question was whether isobenzofuran adduct **25** could be aromatized to hydroquinone **26** with the oxygen bridge intact. Elimination of the oxygen bridge (as water) from **25** would generate a 1,4-anthraquinone group with unfavorable periplanar interactions between phenyl and methoxy substituents. The desired aromatization of **25** to **26** was achieved using potassium *tert*-butoxide followed by quenching with 5% $NaHCO_3$(aq). [Quenching with distilled water instead of bicarbonate produced a red 1,4-anthraquinone group via elimination of the bridge oxygen.] The aromatized, oxygen-bridged product **26** was methylated to give the asymmetrical spacer **27** with a protected bridgehead hydroquinone.[16] To convert this hydroquinone to a bridgehead quinone, a different protecting group can be used for quinone synthon **23**.

The success of Scheme 2 suggests two modifications for Scheme 1: (i) oxidation of *p*-methoxyphenols of **7** using $NaIO_4$ instead of CAN, and (ii) methylation of 1,3-cyclohexadiene adducts (precursor of **9**) at 25 °C instead of at reflux. Scheme 2 also suggests that 1,3-diphenylisobenzofurans (analogous to **24**) are useful dienes for incorporating various bridgehead groups on the concave spacer. Toward the preparation of a fused porphyrin-isobenzofuran diene, tripyrranes **32** and **33** were prepared[17] from novel pyrrole-lactone **28**[18] (eq 2).



Scheme 2

Conditions: (**a**) Piv-Cl (1 eq), pyridine, 4 °C, 96 h. (**b**) $NaIO_4$ (7.5 eq), propionic acid, CH_3CN, H_2O (2:1:1), 0 °C, 2 h. (**c**) (i) 1,3-cyclohexadiene (1.05 eq), Me_2AlCl (0.1 eq), CH_2Cl_2, 0 °C, 75 min; (ii) NaH (3 eq), Me_2SO_4 (3 eq), THF, 25 °C, 2 h. (**d**) NaOMe (4 eq), MeOH; add'n of **20** at 0 °C; 25 °C, 24 h. (**e**) $NaIO_4$ (5 eq), propionic acid, CH_3CN, H_2O (2:1:1), 0 °C, 1 h. (**f**) (i) PhMgBr (2 eq), benzene, Et_2O (3:1), 25 °C, 20 min; reflux, 15 min; (ii) 0 °C, 6 M HCl, 5 min; (iii) CH_2Cl_2 extraction. (**g**) (i) add'n of **24** (1.5 eq) in benzene, Et_2O, CH_2Cl_2, 0 °C; concentrated; (ii) 25 °C, 1 h. (**h**) (i) *tert*-BuOK (3 eq), THF, −50 °C, 15 min; (ii) quench at −50 °C with 5% $NaHCO_3$(aq). (**j**) NaH (3 eq), add'n of **26** at 0 °C, Me_2SO_4 (3 eq), THF, 25 °C, 18 h.
Yields: **18** (72%), **19** (73%), **20** (88%), **21** (97%), **22** (76%), **25** (100%), **26** (100%), **27** (76%).



Conditions: (**a**) Prep'n of **28**: 2,5-dihydrofuran-2-one, TOSMIC (1 eq), Et_2O, DMSO (2:1); dropwise add'n to NaH (2.2 eq); 25 °C, 30 min. (**b**) 1% TFA in CH_2Cl_2, 25 °C, 4.5 days (Ar, dark). (**c**) H_2, 5% Pd(C), THF, Et_3N (1 drop), 25 °C, 18 h. (**d**) TFA, 25 °C, 15 min (Ar). (**e**) $(EtO)_3CH$, TFA (1:2), −23 °C, 20 min (Ar).
Yields: **28** (38%), **30** (59%), **33** (67% from **30**).

Schemes 1 and 2 are useful for syntheses of long-range electron transfer models with a concave spacer. Two important features of concave spacers **9** and **27** are: (i) the spacers control parameters which affect electronic coupling and allow one to systematically vary the intervening medium in the concave space, and (ii) the electronic properties of a spacer can be modulated (e.g., to evaluate the effect on electronic coupling of the spacer itself) by varying the protecting groups for the *p*-hydroquinone moieties of the spacer.

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9. Characterization of **9**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.44-6.42 (m, 4H, H-5,6), 5.36 (s, 2H, H-9), 4.26-4.25 (m (br), 2H, H-1/4), 4.22-4.21 (m (br), 2H, H-1/4), [3.85, 3.78 (s, 3H each, H-13,14)], 3.70 (s, 6H, H-12), 3.36 (s, 2H, H-10), 1.56-1.43 (m, 8H, H-2,3); ^{13}C NMR (67.9 MHz, $CDCl_3$) δ 173.11 (s, C-11), [146.95, 145.36 (s, C-7,8)], [135.75, 135.59 (s, C-1a,4a)], [135.43, 135.28 (d, C-5,6)], [133.41, 130.36 (s, C-7a,8a)], [62.92, 62.76 (q, C-13,14)], 52.07 (q, C-12), 47.47 (d, C-10), [35.09, 34.07, 33.91 (d, C-1,4,9)], [25.40, 25.34 (t, C-2,3)]; IR (KBr) 2978, 2841, 1737, 1474, 1309, 1209, 1190, 1175, 1079 cm^{-1}; MS (EI) *m/e* (%) 599 (M^++1, 11.8), 598 (M^+, 30.0), 570 (9.1), 454 (100.0), 426 (75.2), 411 (27.8), 398 (31.4), 383 (43.3), 368 (12.4), 353 (24.0), 199 (12.0), 184 (12.4); HRMS calcd for $C_{36}H_{38}O_8$ 598.2567, found 598.2569.
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16. Characterization of **27**: ^{1}H NMR (270 MHz, $CDCl_3$) δ 7.85 (d, 1H, J = 7.9 Hz, H-29/40), 7.85 (d, 1H, J = 7.3 Hz, H-29/40), 7.78-7.77 (m, 2H, H-29/40), 7.42-7.33 (m, 6H, H-30,31,41,42), 6.67 (s, 2H, H-34,35), 6.44-6.42 (m, 2H, H-21,22), 5.43 (d, 1H, J = 2.0 Hz, H-9/10), 5.41 (d, 1H, J = 2.1 Hz, H-9/10), 4.26-4.25 (m (br), 1H, H-17/20), 4.22-4.21 (m (br), 1H, H-17/20), [3.85, 3.79 (s, 3H each, H-23,24)], [3.76, 3.69, 3.60, 3.60, (s, 3H each, H-14,16,25,26)], [3.40, 3.35 (s, 3H each, H-43,44)], 3.39-3.34 (m, 2H, H-11,12), 1.59-1.41 (m, 4H, H-18,19); ^{13}C NMR (67.9 MHz, $CDCl_3$) δ [173.02, 172.77 (s, C-13,15)], [147.59, 147.56, 146.90, 146.58, 145.63, 144.96 (s, C-1,4,5,8,33,36)], [140.24, 138.97, 138.81, 136.60, 135.72, 135.46, 134.52, 133.89, 132.74, 130.44, +2 overlapped (s, C-1a,2,3,4a,5a,6,7,8a,28,32,37,39)], [135.53, 135.28 (d, C-21,22)], [130.98, 130.94 (d, C-29,40)], [128.43, 128.38 (d, C-31,42)], [127.20, 127.12 (d, C-30,41)], [112.40, 112.40, (d, C-34,35)], [93.05, 92.98 (s, C-27,38)], [62.88, 62.64 (q, C-23,24)], [62.13, 61.97 (q, C-25,26)], [55.04, 55.04 (q, C-43,44)], [52.23, 52.04 (q, C-14,16)], [47.49, 47.21 (d, C-11,12)], [35.22, 34.81, 34.05, 33.83 (d, C-9,10,17,20)], [25.40, 25.36 (t, C-18,19)]; IR (KBr) 2950, 2830, 1739, 1478, 1471, 1436, 1309, 1252, 1217, 1175, 1083, 999, 992, 802, 774, 696 cm^{-1}; MS (FAB) *m/e* (%) 849 (M^+, 0.9), 460 (2.5), 307 (22.7), 289 (9.9), 154 (100.0), 136 (68.7); HRMS calc'd for $C_{52}H_{48}O_{11}$ 848.3196, found 848.3180. The configuration of **27** is shown as expected (based on **9**); attempted crystallizations were unsuccessful.
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18. Characterization of **28**: ^{1}H NMR (270 MHz, acetone-d_6) δ 11.0 (t (br), NH), 7.30 (d, 1H, J = 1.0 Hz, H-5), 6.78 (s, 1H, H-2), 5.15 (d, 2H, J = 1.0 Hz, CH_2O); ^{13}C NMR (67.9 MHz, acetone-d_6) δ 167.57 (s, CO_2), 133.17 (s, C-3), 116.02 (s, C-4), [115.90, 110.06 (d, C-2,5)], 66.82 (t, CH_2O); IR (KBr) 3389, 3270, 3212, 3176, 3131, 3042, 2958, 1733, 1589, 1523, 1459, 1429, 1344, 1108, 1026, 969, 784, 599 cm^{-1}; MS (EI) *m/e* (%) 124 (M^++1, 4.1), 123 (M^+, 58.2), 122 (M^+−1, 40.0), 94 (68.7).

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