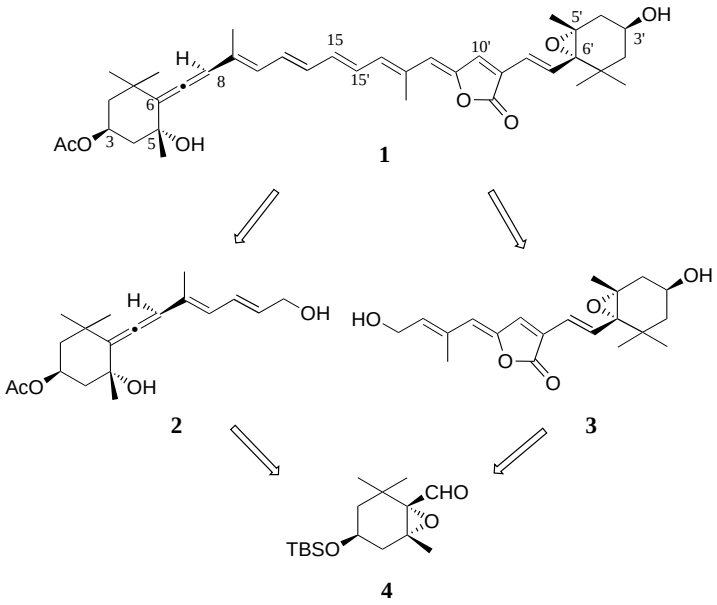
Highly Efficient Stereocontrolled Total Synthesis of the Polyfunctional Carotenoid Peridinin**

Noriyuki Furuichi, Hirokazu Hara, Takashi Osaki, Hajime Mori, and Shigeo Katsumura*

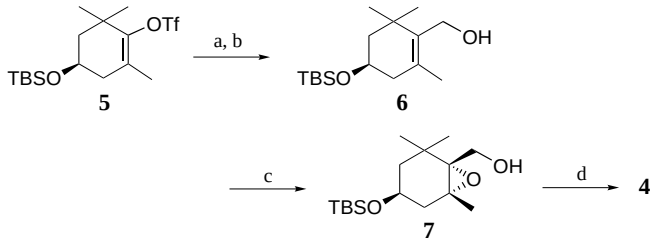
Peridinin (**1**; Scheme 1) was isolated from the planktonic algae dinoflagellates,[1] which causes red tides, and is a carotenoid of an auxiliary light-harvesting pigment for photosynthesis in the sea.[2] The structure of this carotenoid was determined by Lieean-Jensen and co-workers.[3] Peridinin is a unique, highly oxidized C_{37} nor-carotenoid that possesses an allene and a ylidenebutenolide function in the main conjugated polyene chain as well as functionalized cyclohexane rings at both ends of molecule. The synthesis of peridinin was reported by Ito and co-workers in 1993, 100 years after its isolation, and the structure of this unique carotenoid was confirmed.[4] In that synthesis, however, control of stereochemistry and therefore yield were not considered. The stereocontrolled synthesis of peridinin presents several challenges: 1) the stereocontrolled construction of the *all-trans*-conjugated polyene chain that contains the (*Z*)-γ-ylidenebutenolide moiety and the asymmetric allene function, and 2) the stereocontrolled construction of the oxygen functions at the terminal cyclohexane ring. We overcame the problems caused by the instability of the conjugated polyene chain by effectively utilizing our own and/or new synthetic methods in a highly efficient total synthesis of peridinin. The stereochemistry of the six asymmetric carbons and the geometry of six of the seven double bonds in the molecule were controlled.

In the retrosynthetic analysis of peridinin (**1**), we bisected this molecule at the central C15–C15′ double bond (carotenoid numbering). The molecule was thus divided into an allene segment **2** and a ylidenebutenolide segment **3** (Scheme 1). An important intermediate for the syntheses of both segments was the chiral epoxyaldehyde derivative **4**. Complete stereocontrol at the C3, C5, and C6 positions of the terminal cyclohexane ring had not been achieved in previous syntheses of carotenoids. The stereochemistry at these stereogenic carbon atoms was controlled by finding precise reaction conditions for the Sharpless asymmetric epoxidation[5] after



Scheme 1. Polyfunctional carotenoid, peridinin (**1**), and its precursors **2**, **3**, and **4**.

numerous trials. Enantiomerically pure allylic alcohol **6**[6] was prepared from known vinyltriflate **5**[4] by palladium-catalyzed methoxycarbonylation[7] followed by LAH reduction (Scheme 2). Sharpless epoxidation of **6** was realized by the



Scheme 2. Synthesis of **4**: a) CO, $[Pd(PPh_3)_4]$, Et_3N, MeOH, DMF, 70 °C, 15 h (97 %); b) $LiAlH_4$, THF, 45 °C, 20 h (87 %); c) (−)-diethyl-D-tartrate, $Ti(OiPr)_4$, 1.5 M TBHP in toluene, molecular sieves (4 Å), CH_2Cl_2, −20 °C, 30 min (99 %, 92 % *de*); d) $(COCl)_2$, DMSO, CH_2Cl_2, −78 °C, 40 min; Et_3N, 10 min (100 %). DMF = *N*,*N*-dimethylformamide, Tf = trifluoromethanesulfonyl, TBHP = *tert*-butylhydroperoxide.

use of freshly prepared reagents, solvents and exact amounts of the reagents, ((−)-diethyl-D-tartrate (0.3 equivalents), $Ti(OiPr)_4$ (0.2 equivalents), and *tert*-butylhydroperoxide (2.0 equivalents)) at a constant temperature (−20 °C). Under these precise conditions, we obtained the desired α-epoxide **7** in 99 % yield and with 92 % *de*, even on a 10-g scale. The diastereoselectivity under usual conditions for the Sharpless asymmetric epoxidation was 60–70 % *de*. Epoxide **7** was transformed into epoxyaldehyde **4** by means of the Swern oxidation. This is the first example in which the stereochemistry between the C3 hydroxy group and the C5, C6 epoxide in the cyclohexane terminal of carotenoids was satisfactorily controlled.[4, 8]

The stereocontrolled synthesis of the allene segment **2** from **4** is shown in Scheme 3. The preparation of the allylic

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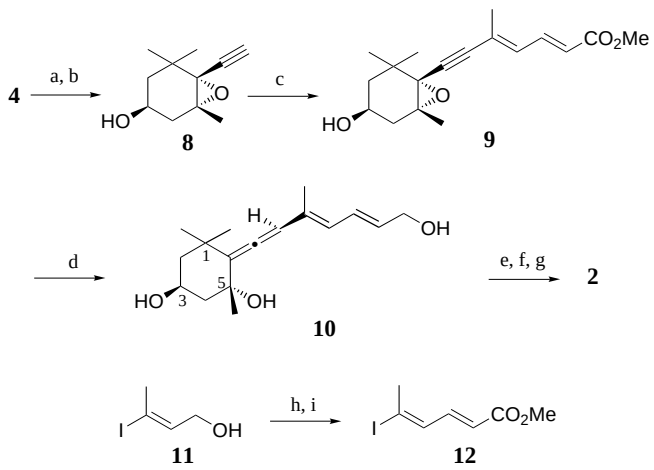
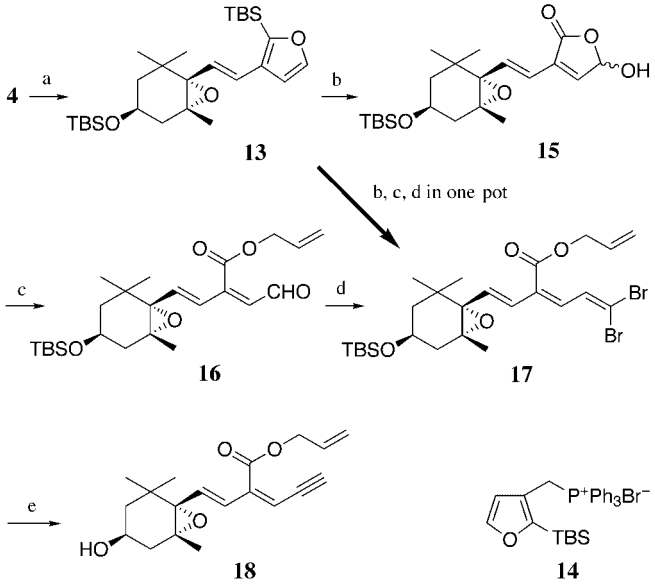


Scheme 3. Synthesis of **2**: a) $ClCH_2P^+Ph_3Cl^-$, *n*BuLi, THF, −30 °C, 3 h; b) *t*BuOK, DMSO, room temperature, 20 min (53% over two steps); c) **12**, $[Pd(PPh_3)_4]$, CuI, iPr_2NH, room temperature, 1 h (84%); d) DIBAL, CH_2Cl_2, 0 °C, 10 min (80%); e) MnO_2, diethyl ether, room temperature, 3 h; f) Ac_2O, pyridine, room temperature, 15 h (86% over two steps); g) $NaBH_4$, MeOH, room temperature 15 min (98%); h) MnO_2, diethyl ether, room temperature, 2 h; i) $(MeO)_2P(O)CH_2CO_2Me$, NaH, THF, room temperature, 5 min (74% over two steps). DMSO = dimethyl sulfoxide, DIBAL = diisobutylaluminum hydride.

hydroxyallene moiety in **10** by means of S_N2' hydride reduction[9] of the conjugated ethynylepoxide group in **9** has been reported. We thus concentrated on the stereocontrolled preparation of **9**. The stereocontrolled construction of the conjugated polyene is the central problem in the synthesis of carotenoids, and palladium-catalyzed $sp-sp^2$ and sp^2-sp^2 is effective. Epoxyaldehyde **4** was transformed into acetylene derivative **8**.[8] Sonogashira cross-coupling[10] of **8** with vinyl iodide **12** (which was prepared from **11**[11]) in the presence of catalytic amounts of tetrakis(triphenylphosphine)palladium and cuprous iodide in diisopropylamine gave the desired ester **9** in 84% yield, with complete stereochemical control. Stereospecific S_N2' reduction of **9** with DIBAL produced triol **10** in 80% yield. The C3 hydroxy group was acetylated by a sequence of regioselective oxidation with MnO_2, acetylation,[12] and then reduction to give **2** with efficient stereocontrol.

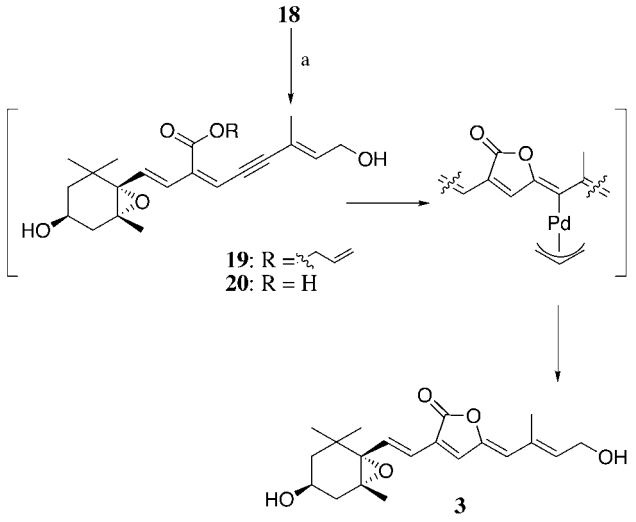
The most striking point in the synthesis of **1** was the preparation of **3**, which includes a characteristic conjugated (*Z*)-γ-ylidenebutenolide function. We have reported a highly stereoselective synthesis of the sesquiterpene freelingyne[13] by means of a Pd^{II}-catalyzed intramolecular lactonization of a conjugated ene-yne carboxylic acid.[14] Analogously, a conjugated ethynylcarboxylic acid such as **20** (which could be obtained from a conjugated (*Z*)-β-alkoxycarbonyldienal such as **16**, Schemes 4 and 5) could serve as a precursor of **3**. We therefore had to synthesize **16** in a stereocontrolled fashion. Thus, epoxyaldehyde **4** was treated with the ylide derived from our silylfurylmethane-Wittig salt **14**[15] to give **13** as a single stereoisomer (Scheme 4). The silylfuran moiety of **13** was chemoselectively oxidized with $^1O_2$[16] to afford the corresponding γ-hydroxybutenolide **15**. The stereocontrolled ring opening of **15** by treatment with ethyldiisopropylamine and allyl bromide in DMSO produced **16** in excellent yield. Aldehyde **16** was transformed into the relatively stable dibromide **17** by the standard method.[17] Dibromide **17** could



Scheme 4. Synthesis of **18**: a) **14**, *n*BuLi, diethyl ether, 0 °C, 3 h; b) O_2, TPP, CH_2Cl_2, *hν*, −78 °C, 30 min (77% over two steps); c) iPr_2EtN, DMSO, room temperature, 3 h, then allyl bromide, room temperature, 1 h (70%); d) CBr_4, PPh_3, Et_3N, CH_2Cl_2, −60 °C, 1 h (89%); e) TBAF, THF, 45 °C, 20 h (81%). TPP = 5,10,15,20-tetraphenyl-21*H*,23*H*-porphine, TBAF = tetra-*n*-butylammonium fluoride.

also be obtained from **13** in a one-pot procedure: treatment of **13** with $^1O_2$, allyl ester formation, and dibromide formation in CH_2Cl_2 gave **17** in 53% overall yield from **4**. Dibromide **17** was transformed into **18** in 81% yield by treatment with TBAF.[18]

The novel and efficient one-pot stereocontrolled formation of **3** from **18** was the highlight of our synthesis (Scheme 5). A mixture of allyl ester **18** (Scheme 4) and vinyl iodide **11** (Scheme 3, 1 equivalent) was stirred in the presence of catalytic amounts of tetrakis(triphenylphosphine)palladium and cuprous iodide in triethylamine at room temperature for 1 h. After the complete consumption of **18** was ascertained by TLC, formic acid was added to the reaction mixture at room



Scheme 5. Synthesis of **3**: a) **11**, $[Pd(PPh_3)_4]$, CuI, Et_3N, room temperature, 1 h; HCO_2H, room temperature, 20 h (49%).

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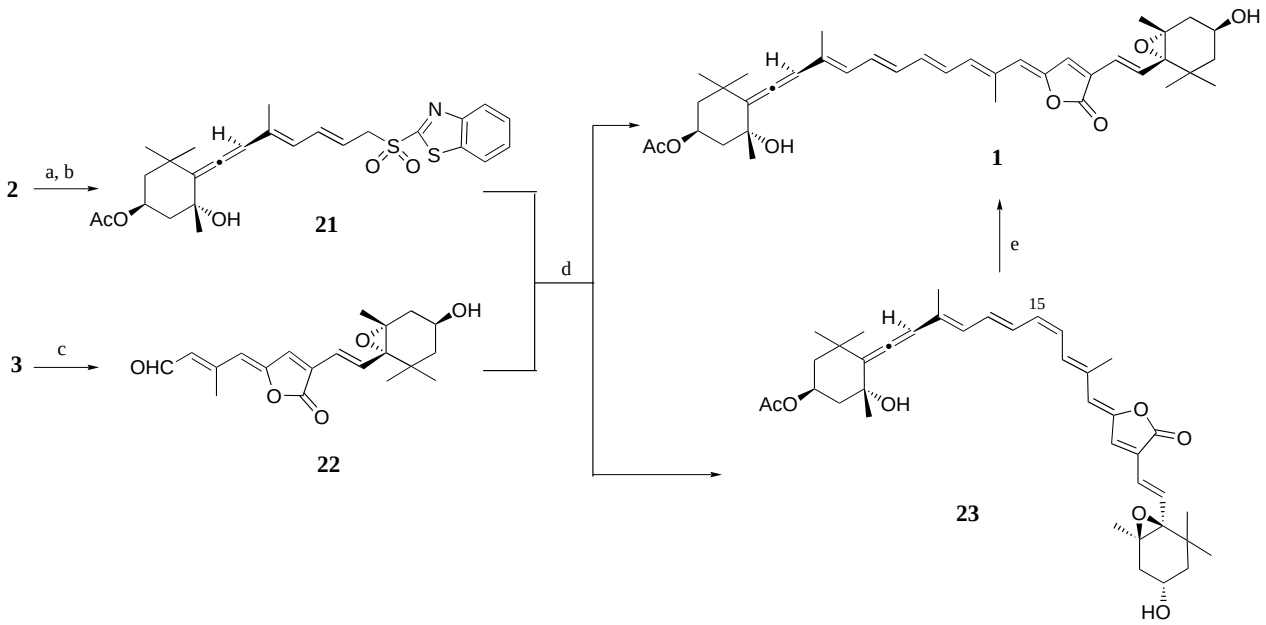

Scheme 6. Total synthesis of **1**: a) 2-mercaptobenzothiazole, PPh_3, DIAD, THF, room temperature, 1.5 h (78%); b) $(NH_4)_6Mo_7O_{24}\cdot 4H_2O$, H_2O_2 (aq. 30%), EtOH, 0 °C, 1 h (89%); c) MnO_2, diethyl ether, room temperature, 5 min; d) NaHMDS, THF, −78 °C, 5 min, in the dark (50% from **22**, *E*/*Z* 1:3); e) C_6H_6, 25 °C, 3 d, in the dark (*E*/*Z* > 5:1); preparative HPLC purification. DIAD = diisopropyl azodicarboxylate, NaHMDS = sodium bis(trimethylsilyl)amide, HPLC = high-performance liquid chromatography.

temperature, and the resulting mixture was stirred for 20 h. As expected, we obtained the desired ylidenebutenolide **3** in 49% yield as a single stereoisomer. Sonogashira coupling of **18** with **11**, reductive deallylation,[19] and highly stereoselective intramolecular lactonization proceeded successfully via **19** in one pot[20] by the successive action of Pd^0 and Pd^{II} catalysts.

The final step in the synthesis of peridinin was the coupling of **2** and **3**. After several trials, we knew that the halides derived from the C_{17}-allene segment **2** were unstable under the reaction conditions required for the preparation of the corresponding Wittig salt, although the very similar C_{15}-Wittig salt has been reported.[20] We thus turned our attention to the modified Julia–Kocienski olefination,[21] which made the olefination possible at a relatively lower temperature. Allene **2** was transformed into benzothiazole sulfone **21** by the Mitsunobu reaction with 2-mercaptobenzothiazole, followed by molybdenum(VI)-catalyzed oxidation[22] (Scheme 6). The reaction between the sulfone group of **21** and the aldehyde function of **22** (derived from **3**) proceeded successfully within 5 min by using NaHMDS at −78 °C in the dark. Although the crude product obtained was a mixture of the desired *all-trans*-peridinin (**1**) and its 15-*cis* isomer **23** (1:3 based on ^{1}H NMR spectroscopic analysis), we found that the *Z* isomer was converted into the thermodynamically more stable *E* isomer in a solution of benzene at room temperature in the dark after 3 days (*E*/*Z* > 5:1 based on ^{1}H NMR spectroscopic analysis and analytical HPLC). The desired enantiomerically pure peridinin (**1**) was obtained after purification by means of preparative HPLC in the dark. The spectral data of the synthetic peridinin were in good agreement with those reported.[3, 4]

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[1] F. Schutt, *Ber. Dtsch. Bot. Ges.* **1890**, *8*, 9.

[2] a) H. A. Frank, R. J. Cogdell in *Carotenoids in Photosynthesis* (Eds.: A. Young, G. Britton), Chapman & Hall, London, **1993**; b) E. Hofmann, P. M. Wrench, F. P. Sharples, R. G. Hiller, W. Welte, K. Diederichs, *Science* **1996**, *272*, 1788.

[3] a) H. H. Strain, W. A. Svec, K. Aitzetmuller, M. C. Grandolfo, J. J. Katz, H. Kjosen, S. Norgard, S. Lieean-Jensen, F. T. Haxo, P. Wegfahrt, H. Rapoport, *J. Am. Chem. Soc*. **1971**, *93*, 1823; b) J. E. Johansen, G. Borch, S. Lieean-Jensen, *Phytochemistry* **1980**, *19*, 441.

[4] a) Y. Yamano, M. Ito, *J. Chem. Soc. Perkin Trans. 1* **1993**, 1599; b) M. Ito, Y. Yamano, S. Sumiya, A. Wada, *Pure Appl. Chem.* **1994**, *66*, 939.

[5] a) T. Katsuki, K. B. Sharpless, *J. Am. Chem. Soc*. **1980**, *102*, 5976; b) R. M. Hanson, K. B. Sharpless, *J. Org. Chem*. **1986**, *51*, 1922; c) Y. Gao, R. M. Hanson, J. M. Klunder, S. Y. Ko, H. Masamune, K. B. Sharpless, *J. Am. Chem. Soc*. **1987**, *109*, 5765.

[6] Y. Yamano, C. Tode, M. Ito, *J. Chem. Soc. Perkin Trans. 1* **1998**, 2569.

[7] a) A. Schoenberg, I. Bartoletti, R. F. Heck, *J. Org. Chem*. **1974**, *39*, 3318; b) J. K. Stille, P. K. Wong, *J. Org. Chem*. **1975**, *40*, 532; c) M. Hidai, T. Hikita, Y. Wada, Y. Furikura, Y. Uchida, *Bull. Chem. Soc. Jpn*. **1975**, *48*, 2075.

[8] A. Baumeler, W. Brade, A. Haag, C. H. Eugster, *Helv. Chim. Acta*. **1990**, *73*, 700.

[9] E. Widmer, *Pure Appl. Chem*. **1985**, *57*, 741; alternatively, we reported the novel synthesis of the allene moiety of carotenoids by means of biomimetic photosensitized oxygenation: M. Nakano, N. Furuichi, H. Mori, S. Katsumura, S. *Tetrahedron Lett.* **2001**, *42*, 7307.

[10] K. Sonogashira in *Comprehensive Organic Synthesis*, *Vol. 3* (Eds.: B. M. Trost, I. Fleming, G. Pattenden), Pergamon, Oxford, **1991**, p. 521.

[11] Vinyl iodide **12** was prepared from the commercially available 2-butyn-1-ol by means of stannylcupration with nBu$_3$Sn(nBu)CuCN-Li$_2$ (B. H. Lipshutz, J. A. Kozlowski, R. S. Wilhelm, *J. Org. Chem*. **1984**, *49*, 3943) followed by tin–halogen exchange.

[12] Y. Yamano, S. Sumiya, M. Ito, *J. Chem. Soc. Perkin Trans. 1* **1995**, 167.

[13] H. Mori, H. Kubo, H. Hara, S. Katsumura, *Tetrahedron Lett.* **1997**, *38*, 5311.

[14] Original reports: a) C. Lambert, K. Utimoto, H. Nozaki, *Tetrahedron Lett*. **1984**, *25*, 5323; b) X. Lu, X. Huang, S. Ma, *Tetrahedron Lett*. **1993**, *34*, 5963; this method was developed for natural products syntheses by other groups: c) M. Kotora, E. Negishi, *Tetrahedron Lett*. **1996**, *37*, 9041; d) F. Liu, E. Negishi, *J. Org. Chem*. **1997**, *62*, 8591; e) M. Kotora, E. Negishi, *Synthesis* **1997**, 121; f) E. Negishi, M. Kotora, *Tetrahedron*

1997, *53*, 6707; g) R. Rossi, F. Bellina, M. Biagetti, L. Mannina, *Tetrahedron Lett.* **1998**, *39*, 7799; h) C. Xu, E. Negishi, *Tetrahedron Lett.* **1998**, *40*, 431; i) R. Rossi, F. Bellina, A. Catanese, L. Mannina, D. Valensin, *Tetrahedron* **2000**, *56*, 479.

[15] a) K. Tanaka, M. Kamatani, H. Mori, S. Fujii, K. Ikeda, M. Hisada, Y. Itagaki, Y, S. Katsumura, *Tetrahedron* **1999**, *55*, 1657; b) T. Hata, K. Tanaka, S. Katsumura, *Tetrahedron Lett.* **1999**, *40*, 1731; c) N. Furuichi, T. Hata, H. Soetjipto, M. Kato, S. Katsumura, *Tetrahedron* **2001**, *57*, 8425.

[16] S. Katsumura, K. Hori, S. Fujiwara, S. Isoe, *Tetrahedron Lett.* **1985**, *26*, 4625.

[17] a) E. J. Corey, P. L. Fuchs, *Tetrahedron Lett.* **1972**, *13*, 3769; b) D. Grandjean, P. Pale, J. Chuche, *Tetrahedron Lett.* **1994**, *35*, 3529.

[18] a) F. Naso, L. Ronzini, *J. Chem. Soc. Perkin Trans. 1* **1974**, 340; b) K. C. Nicolaou, C. V. C. Prasad, P. K. Somers, C.-K. Hwang, *J. Am. Chem. Soc.* **1989**, *111*, 5330; c) I. C. Gonzalez, C. J. Forsyth, *J. Am. Chem. Soc.* **2000**, *122*, 9099.

[19] a) T. Mandai, K. Ohta, N. Baba, M. Kawada, J. Tsuji, *Synlett* **1992**, 671; b) C. J. Solomon, E. G. Mata, O. A. Mascaretti, *Tetrahedron* **1993**, *49*, 3714; c) J. Tsuji, T. Mandai, *Synthesis* **1996**, 1.

[20] Y. Yamano, C. Tode, M. Ito, *J. Chem. Soc. Perkin Trans. 1* **1995**, 1895.

[21] a) J. B. Baudin, G. Hareau, S. A. Julia, O. Ruel, *Tetrahedron Lett.* **1991**, *32*, 1175; b) J. B. Baudin, G. Hareau, S. A. Julia, O. Ruel, *Bull. Soc. Chim. Fr.* **1993**, *130*, 336; c) J. B. Baudin, G. Hareau, S. A. Julia, R. Lorne, O. Ruel, *Bull. Soc. Chim. Fr.* **1993**, *130*, 856; d) P. R. Blakemore, W. J. Cole, P. J. Kocienski, A. Morley, *Synlett* **1998**, *1*, 26.

[22] H. S. Schultz, H. B. Freyermuch, S. R. Buc, *J. Org. Chem.* **1963**, *28*, 1140.

Dynamics and Energetics of Hole Trapping in DNA by 7-Deazaguanine**

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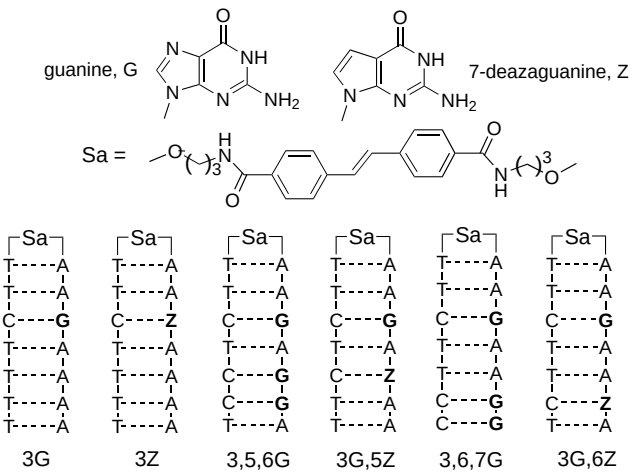
Oxidative cleavage of DNA by photonucleases can occur at sites separated from the nuclease by as many as several dozen base pairs.[1–4] Such long-distance processes are known to occur by a multistep hole-hopping mechanism which is initiated by photoinduced electron transfer between the nuclease (electron acceptor) and a neighboring base (electron donor) resulting in creation of a hole on the base. Migration of the hole over long distances is more rapid than the chemical reactions of the oxidized bases which lead to strand cleavage.[5] Strand cleavage occurs selectively at guanine, the most readily oxidized of the nucleobases, and is sequence selective.[6, 7] Preferential cleavage at GG and GGG sequences has been attributed to stabilization of the hole by delocalization over two or three guanine residues.[8–10]

We recently reported the use of transient absorption spectroscopy with kinetic modeling to obtain the rate constants for reversible hole transports between $G^{\bullet+}$ and GG or GGG sequences separated by a single A:T base pair.[11, 12] The resulting Gibbs energy differences, 52 mV for GG and 77 mV for GGG, are much smaller than those previously estimated from calculations of gas-phase ionization potentials.[8] However, recent theoretical studies by Bixon and Jortner[13, 14] and by Kurnikov et al.[15] have provided results in good agreement with our experimental data. Our kinetic data have also been used by Giese and coworkers[5, 16] to model the results of strand-cleavage studies in duplexes containing G, GG, and GGG sites.

The importance of obtaining experimental values for the dynamics and energetics of hole transport in DNA led us to investigate the use of the modified nucleobase 7-deazaguanine, Z, as a hole trap. The oxidation potential of Z is reported to be 0.3 eV lower than that of G.[17] Z has been employed in investigations of single-step (superexchange) electron transfer in DNA.[18–20] Both Z and 8-oxoguanine, which also has a lower oxidation potential than G, have been used as hole traps in strand cleavage studies.[6, 21] We report here the results of an investigation of the dynamics of forward and return hole transport from G to Z, which establish that Z is a much deeper hole trap than GG or GGG. In addition, the dynamics of the hole transport processes are found to be strongly dependent upon the number of A:T base pairs separating the hole donor and acceptor.

The structures of the synthetic DNA hairpins prepared for the present study are shown in Scheme 1. The stilbene-4,4′-dicarboxamide (Sa) serves as a linker connecting complementary polyT and polyA arms containing one or more C:G or C:Z base pairs.[22] All of these hairpins have high melting temperatures (>75 °C) and circular dichroism spectra similar to that of a stilbene-linked hairpin known to adopt a normal B-form structure in which the stilbene is parallel to the



Scheme 1. Structures of the synthetic DNA hairpins used in this study.

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