ceeds in a catalytic mode, it requires strict reaction conditions and suffers from low *trans/cis* selectivity ($\approx 3/1$). The present asymmetric aziridination is a stoichiometric reaction but may represent a promising general[16] and practical approach to optically active functionalized aziridines due to its compatibility to a wide range of substrates, high yields, and very mild reaction conditions. Furthermore, the ylide precursors (chiral sulfides) could be easily recovered in higher than 80 % yields without loss of optical purity and reused. Though the *ee* value of the product is not very high (maximum 84.9 %, reaction 6), it can be efficiently improved by a single recrystallization from *n*-hexane; this may offer a practical utility of these products. For example, the *ee* values of the products from reactions 3 and 4 can be increased from 69.5 % to 96.6 % and from 77.5 % to 99.1 % for yields of 58 % and 52 %, respectively. The opposite asymmetric induction was achieved with sulfonium salts containing *exo*-sulfido groups (**3**, reactions 1-8) to provide (2*R*)-(−)-aziridines and *endo*-sulfido groups[17] (**4** and **5**, reactions 9-14) to provide (2*S*)-(+)-aziridines. Chiral acetylenylaziridines are very difficult to prepare by the two direct approaches based on carbene, nitrene, or aza-Darzens reaction.[18]

## *Experimental Section*

General procedure for aziridination: **2** (0.5 mmol), the chiral sulfonium salt **3**, **4**, or **5** (0.6 mmol), and $Cs_2CO_3$ (0.6 mmol) were mixed and stirred in $CH_2Cl_2$ (3 mL, reagent grade, used directly without drying) at room temperature in air. After the reaction was completed (TLC, 2–5 h), the reaction mixture was filtered through a short silica-gel column to remove inorganic salts. The filtrate was concentrated and purified by chromatography on a silica-gel column with petroleum ether(60–90 °C) and ethyl acetate (4:1) as the eluent to give pure (-)- or (+)- *N*-sulfonyl acetylenylaziridines **1**. Chiral sulfides **6**, **7**, or **8** were also recovered (> 80 % yields).

**3**, **4**, or **5**: A mixture of a chiral sulfide [14] **6**, **7**, or **8** (2.004 g, 10 mmol) and 3-trimethylsilylpropargyl bromide [19] (2.294 g, 12 mmol) in acetone (3 mL) was stirred at room temperature for 6–48 h. Most of acetone was removed under reduced pressure, and the residue collected by filtration, washed with dry ether (3 × 40 mL), and dried under vacuum at room temperature to give the desired sulfonium salt as a white solid. It was used directly without further purification.

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[1] a) D. Tanner, *Angew. Chem.* **1994**, *106*, 625; *Angew. Chem. Int. Ed. Engl.* **1994**, *33*, 599; b) *Pure Appl. Chem.* **1993**, *65*, 1319; c) T. Hudlicky, G. Seoane, J. D. Price, K. G. Gadamasetti, *Synlett* **1990**, 433.

[2] a) D. A. Evans, M. M. Faul, M. T. Bilodeau, B. A. Anderson, D. M. Barnes, *J. Am. Chem. Soc.* **1993**, *115*, 5328; b) Z. Li, K. R. Conser, E. N. Jacobsen, *ibid.* **1993**, *115*, 5326.

[3] a) R. S. Atkinson, W. T. Gattrell, A. P. Ayscough, T. M. Raynham, *Chem. Commun.* **1996**, 1935; b) R. S. Atkinson, M. P. Coogan, I. S. T. Lochrie, *Tetrahedron Lett.* **1996**, *37*, 5179; c) J. T. Kapron, B. D. Santarsiero, J. C. Vederas, *J. Chem. Soc. Chem. Commun.* **1993**, 1074; d) J. Aires-de-Sousa, A. M. Lobo, S. Prabhakar, *Tetrahedron Lett.* **1996**, *37*, 3183.

[4] N. Furukawa, T. Yoshimura, M. Ohtsu, T. Akasaka, S. Oae, *Tetrahedron* **1980**, *36*, 73.

[5] K. B. Hansen, N. S. Finney, E. N. Jacobsen, *Angew. Chem.* **1995**, *107*, 750; *Angew. Chem. Int. Ed. Engl.* **1995**, *34*, 676.

[6] a) F. A. Davis, P. Zhou, G. V. Reddy, *J. Org. Chem.* **1994**, *59*, 3243; b) F. A. Davis, H. Liu, G. V. Reddy, *Tetrahedron Lett.* **1996**, *37*, 5473; c) J. L. G. Ruano, I. Fernandez, C. Hamdouchi, *ibid.* **1995**, *36*, 295; d) F. A. Davis, P. Zhou, C.-H. Liang, R. E. Reddy, *Tetrahedron: Asymmetry* **1995**, *6*, 1511; e) J. L. G. Ruano, I. Fernandez, M. D. P. Catalina, A. A. Cruz, *ibid.* **1996**, *7*, 3407.

[7] T. Satoh, T. Sato, T. Oohara, K. Yamakawa, *J. Org. Chem.* **1989**, *54*, 3973.

[8] Asymmetric epoxidation: a) D. Yang, Y.-C. Yip, M.-W. Tang, M.-K. Wong, J.-H. Zheng, K.-K. Cheung, *J. Am. Chem. Soc.* **1996**, *118*, 491; b) V. K. Aggarwal, M. F. Wang, *Chem. Commun.* **1996**, 191; c) Y. Tu, Z.-X. Wang, Y. Shi, *J. Am. Chem. Soc.* **1996**, *118*, 9806.

[9] M. P. Doyle in *Catalytic Asymmetric Synthesis* (Ed.: I. Ojima), VCH, Weinheim, **1993**, p. 63.

[10] Review on asymmetric aziridination: A.-H. Li, L.-X. Dai, *Chemistry (The Chinese Chem. Soc., Taipei)* **1996**, *54*, 157 (Chinese).

[11] Insertion of nitrene into an allylic C–H bond was observed by the reaction with an aliphatic alkene: P. Müller, C. Baud, Y. Jacquier, *Tetrahedron* **1996**, *52*, 1543, and references therein.

[12] V. K. Aggarwal, A. Thompson, R. V. H. Jones, M. C. H. Standen, *J. Org. Chem.* **1996**, *61*, 8368; for a corresponding epoxidation, see V. K. Aggarwal, J. G. Ford, A. Thompson, R. V. H. Jones, M. C. H. Standen, *J. Am. Chem. Soc.* **1996**, *118*, 7004.

[13] a) A.-H. Li, L.-X. Dai, X.-L. Hou, *Chem. Commun.* **1996**, 491; b) *J. Chem. Soc. Perkin Trans. 1* **1996**, 867; c) A.-H. Li, L.-X. Dai, X.-L. Hou, M.-B. Chen, *J. Org. Chem.* **1996**, *61*, 4641; d) A.-H. Li, L.-X. Dai, X.-L. Hou, *J. Chem. Soc. Perkin Trans. 1* **1996**, 2725.

[14] A.-H. Li, L.-X. Dai, X.-L. Hou, Y.-Z. Huang, F.-W. Li, *J. Org. Chem.* **1996**, *61*, 489.

[15] Z.-L. Zhou, Y.-Z. Huang, L.-L. Shi, J. Hu, *J. Org. Chem.* **1992**, *57*, 6598.

[16] We have shown that *N*-sulfonylimine-based aziridination is applicable to either semistable (including allylic, propargylic, and benzylic), reactive (simple alkyl ylides), and stabilized ylides (substituted with electron-withdrawing groups). Other reactive imines and activation methods of common imines also undergo this aziridination reaction.

[17] Prepared according to literature methods: a) R. J. Goodridge, T. W. Hambley, R. K. Haynes, D. D. Ridley, *J. Org. Chem.* **1988**, *53*, 2881; b) see also ref. [14].

[18] Rearrangement of an acetylenyl-substituted vinylaziridine by a multistep sequence: a) N. Manisse, J. Chuche, *Tetrahedron* **1977**, *33*, 2399; b) *J. Am. Chem. Soc.* **1977**, *99*, 1272.

[19] T. K. Jones, S. E. Denmark, *Org. Synth.* **1990**, *7*, 524.

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# Synthesis of Taxoid Ring Systems: AC → ABC Approach by Way of Intramolecular Alkylation[**]

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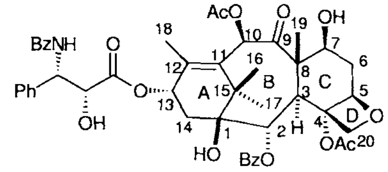
Kensuke Nagashima, Tadashi Okabe, and
Takayuki Doi



**1**

Taxol (**1**) is an attractive molecular target both in terms of its biological activity and its synthetic complexity, which includes a conformationally restricted ABCD ring system bearing many stereogenic centers with interesting functional groups.[1–3] We have focused on the development of a method for constructing the B ring of the taxoid system.[4] There are several methods for the preparation of medium-membered rings, however, it has been difficult to effect direct cyclization of eight-membered rings due to entropic and enthalpic effects.[5] This is especially true, if the conformation of the desired cyclic molecule is restricted in a highly strained conformation, such as in the taxoid system, thereby making the preparation of the ring from a strain-free acyclic compound even more difficult. We have previously reported several methods for overcoming this problem; for example, the contraction of large-membered ring molecules and the intramolecular alkylation of cyanohydrin ethers with alkyl iodides, tosylates, and allylic halides, efficiently form 10-

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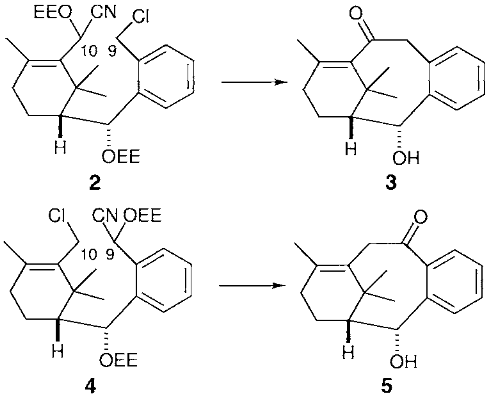
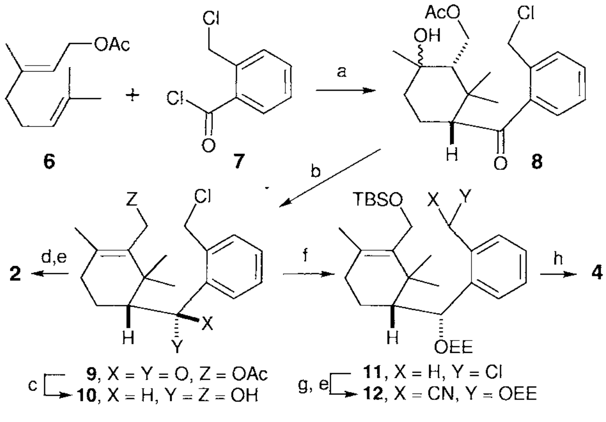
to 15-membered rings.[6, 7] Herein, we report the efficient formation of the eight-membered B ring of the taxoid system by the latter method.



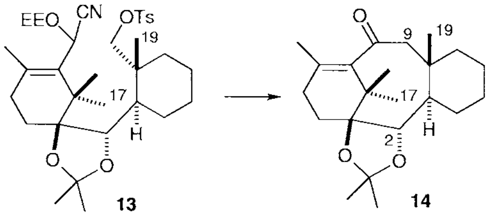
Scheme 1. Construction of the B ring in an aromatic taxoid system by intramolecular cyclization. EE = ethoxyethyl.



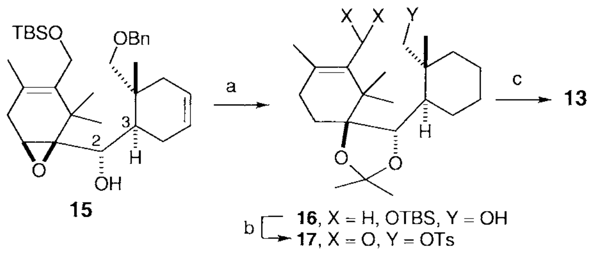
Scheme 2. a) $AlCl_3$, $CH_2Cl_2$, 0°C, 5 h, 61%; b) $HC(OMe)_3$, p-TsOH, 25°C, 5 h, 51% + 31% (isomer); c) diisobutyl aluminum hydride (DIBAL), $CH_2Cl_2$, −78°C, 30 min, 91%; d) $MnO_2$, PhH, 25°C, 44% (recovery of starting material: 40%); e) TMS(CN), [18]crown-6 KCN; 1N HCl, THF; p-TsOH, ethylvinyl ether (EVE), 84–88% in three steps; f) TBSCl, DMF, imidazole; PPTS, EVE, $CH_2Cl_2$-PhH, 91% (two steps); g) DMSO, $NaHCO_3$, 110°C, 10 h, 77%; h) TBAF, THF; MsCl, $NEt_3$, $CH_2Cl_2$; LiCl, THF, 79% (two steps).

Scheme 1 summarizes our initial study on the formation of the B ring of the taxoid system, in which the CD rings are replaced with an aromatic ring. We planned to cyclize the B ring at positions C9 and C10 by applying an intramolecular cyanohydrin alkylation. In this respect, it was important to determine the feasibility of the alkylation of C10 in **2** by C9 and that of C9 in **4** by C10, which should lead to **3** and **5**, respectively. The syntheses of **2** and **4** are shown in Scheme 2. The Friedel–Crafts reaction of geranyl acetate (**6**) with *ortho*-(chloromethyl)benzoyl chloride (**7**) gave a diastereomer mixture of **8** by acid-catalyzed olefin cyclization.[8] Dehydration of the tertiary alcohol in **8** provided tetrasubstituted alkene **9** in 51% yield, together with an *endo* isomeric alkene (30%). Stereoselective reduction of the ketone in **9** and deprotection of the acetate using DIBAL furnished diol **10** in 91% yield. Selective oxidation of the allylic alcohol gave the enal, which was converted to the protected cyanohydrin ether **2** in three steps (84% overall yield). The cyclization precursor **4** was also prepared from **10**: Selective protection of the primary alcohol of **10** with *tert*-butyldimethylsilyl chloride (TBSCl), followed by protection of the secondary alcohol with EVE gave **11** in 91% yield. Oxidation of **11** with DMSO afforded the aldehyde, which was converted to the protected cyanohydrin ether **12** as previously described. Deprotection of the TBS group in **12**, followed by chlorination afforded the cyclization precursor **4** in 79% overall yield.

The closure of the eight-membered ring in **2** and **4** was achieved by intramolecular alkylation (Scheme 1). Treatment of **2** or **4** with $LiN(SiMe_3)_2$ in THF at 80°C immediately produced the cyclized products in 93 and 89% yields, respectively. The products underwent sequential hydrolysis with acid and base leading to the desired cyclic ketones **3** and **5** in 80% and 95% yields, respectively.[9] The structure of **3** was unambiguously determined by X-ray crystallographic analysis.[10] Thus, we have found that intramolecular alkylation of cyanohydrin ethers can form the eight-membered ring in both directions (C10 → C9, C9 → C10) leading to ABC taxoids with an aromatic C ring.



Scheme 3. Construction of the B ring in a nonaromatic taxoid system by intramolecular cyclization.



Scheme 4. a) $LiAlH_4$, ether, 25°C, 82%; isopropenyl methyl ether, camphorsulfonic acid (CSA), $CH_2Cl_2$, 0°C, quant.; $Pd(OH)_2$, $H_2$, AcOEt, 25°C, 16 h, 89%; b) TsCl, Py, 25°C, 14 h, quant.; tetrabutylammonium fluoride (TBAF), THF, 25°C, 18 h, 93%; tetrapropylammonium perruthenate (TPAP), 4-methylmorpholine *N*-oxide (NMO), 25°C, 5 h, 76%; c) TMS(CN), [18]crown-6 KCN; 1N HCl, THF; p-TsOH, EVE, $CH_2Cl_2$, 59% (three steps).

We then examined whether this method could be applied to the formation of taxoid system **14** with a nonaromatic C ring (Scheme 3). The cyclization of **13** must overcome the transannular interactions of the dimethyl groups (17-Me and 19-Me) which are close during the construction of the B ring. We prepared the cyclization precursor **13** as follows (Scheme 4): According to the reported method,[11, 12] the epoxide **15** was obtained by the coupling reaction of a vinyllithium species corresponding the A ring moiety with *trans*-6-benzyloxylmethyl-6-methyl-3-cyclohexenecarboxaldehyde.[13] Reduction of **15** with $LiAlH_4$,[11] followed by protection of the resulting 1,2-diol, gave the corresponding acetonide, whose hydrogenation and concomitant deprotection of the benzyl ether furnished alcohol **16**. Tosylation of the neopentyl function in **16**, followed by deprotection of TBS provided the allylic alcohol, which was oxidized by TPAP[14] to afford enal **17** in 71% overall yield. The cyanohydrin ether **13** was prepared from **17** analogous to step

(e) in Scheme 2. Intramolecular alkylation of **13** proceeded in 70% yield by using $LiN(SiMe_3)_2$ in refluxing dioxane (Scheme 3). Treatment of the cyclized products with acid followed by base gave the desired cyclic enone **14** in 58% overall yield (based on **13**). The stereochemistry of **14** was fully consistent with the NMR data and was confirmed unequivocally by NOE difference spectroscopy.[15] It is noteworthy that the intramolecular alkylation using cyanohydrin anions overcame not only the transannular interactions in the formation of the taxoid B ring but also the steric hindrance in the alkylation at the neopentyl position.

In summary, we have demonstrated that the intramolecular alkylations of the cyanohydrin ethers are effective for the formation of the B ring of the taxoid systems with not only aromatic but also nonaromatic C rings.

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[1] M. C. Wani, H. L. Taylor, M. E. Wall, P. Coggon, A. T. McPhail, *J. Am. Chem. Soc.* **1971**, *93*, 2325-2327.

[2] R. A. Holton, C. Somoza, H.-B. Kim, F. Liang, R. J. Biediger, P. D. Boatman, M. Shindo, C. C. Smith, S. Kim, H. Nadizadeh, Y. Suzuki, C. Tao, P. Vu, S. Tang, P. Zhang, K. K. Murthi, L. N. Gentile, J. H. Liu, *J. Am. Chem. Soc.* **1994**, *116*, 1597-1598; R. A. Holton, H.-B. Kim, C. Somoza, F. Liang, R. J. Biediger, P. D. Boatman, M. Shindo, C. C. Smith, S. Kim, H. Nadizadeh, Y. Suzuki, C. Tao, P. Vu, S. Tang, P. Zhang, K. K. Murthi, L. N. Gentile, J. H. Liu, *ibid.* **1994**, *116*, 1599-1600; K. C. Nicolaou, Z. Yang, J.-J. Liu, H. Ueno, P. G. Nantermet, R. K. Guy, C. F. Claiborne, J. Renaud, E. A. Couladouros, K. Paulvannan, E. J. Sorensen, *Nature* **1994**, *367*, 630-634; J. J. Masters, J. T. Link, L. B. Snyder, W. B. Young, S. J. Danishefsky, *Angew. Chem.* **1995**, *107*, 1886-1888; *Angew. Chem. Int. Ed. Engl.* **1995**, *34*, 1723-1726.

[3] C. S. Swindell, *Studies in Natural Products Chemistry, Vol. 12*, Elsevier, New York, **1993**, pp. 179-231; K. C. Nicolaou, W. M. Dai, R. K. Guy, *Angew. Chem.* **1994**, *106*, 38-69; *Angew. Chem. Int. Ed. Engl.* **1994**, *33*, 15-44.

[4] Routes to taxoid B ring: A. S. Kende, S. Johnson, P. Sanfilippo, J. C. Hodges, L. N. Jungheim, *J. Am. Chem. Soc.* **1986**, *108*, 3513-3515; M. H. Kress, R. Ruel, W. H. Mijjer, Y. Kishi, *Tetrahedron Lett.* **1993**, *34*, 5999-6002; J. J. Masters, D. K. Jung, W. G. Bornmann, S. J. Danishefsky, *ibid.* **1993**, *34*, 7253-7256; C. S. Swindell, W. Fan, *ibid.* **1996**, *37*, 2321-2324; R. Hara, T. Furukawa, Y. Horiguchi, I. Kuwajima, *J. Am. Chem. Soc.* **1996**, *118*, 9186-9187.

[5] For the synthesis of carbocyclic eight-membered rings see N. A. Petasis, M. A. Patane, *Tetrahedron* **1992**, *48*, 5757-5821.

[6] T. Doi, T. Takahashi, *J. Org. Chem.* **1991**, *56*, 3465-3467.

[7] T. Takahashi, H. Nemoto, J. Tsuji, *Tetrahedron Lett.* **1983**, *24*, 2005-2008; T. Takahashi, T. Nagashima, J. Tsuji, *ibid.* **1981**, *22*, 1359-1362; G. Stork, J. C. Depezay, J. d'Angelo, *ibid.* **1975**, 389-392.

[8] T. Kumagai, F. Ise, T. Uyehara, T. Kato, *Chem. Lett.* **1981**, 25-28; T. Kato, H. Takayanagi, T. Suzuki, T. Uyehara, *Tetrahedron Lett.* **1978**, 1201-1204.

[9] Spectral data in agreement with the reported structures were obtained for all compounds in this paper.

[10] 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-100231. Copies of the data can be obtained free of charge on application to The Director, CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: int. code +(1223) 336-033; e-mail deposit@chemcrys.cam.ac.uk).

[11] K. C. Nicolaou, Z. Yang, E. J. Sorensen, M. Nakada, *J. Chem. Soc. Chem. Commun.* **1993**, 1024-1026; K. C. Nicolaou, C. F. Claiborne, P. G. Nantermet, E. A. Couladouros, E. J. Sorensen, *J. Am. Chem. Soc.* **1994**, *116*, 1591-1592.

[12] M. J. D. Grandi, D. K. Jung, W. J. Krol, S. J. Danishefsky, *J. Org. Chem.* **1993**, *58*, 4989-4492.

[13] The less polar **15** was isolated from a 4:1 mixture of diastereomers produced by the coupling reaction by chromatography on silica gel. The stereochemistry at the 2 position was determined after cyclization.

[14] W. P. Griffith, S. V. Ley, *Aldrichimica Acta* **1990**, *23*, 13.

[15] **14**: $^1H$ NMR (270 MHz, $CDCl_3$): $\delta = 3.93$ (1H, d, $J = 5.0$ Hz), 2.6-2.8 (1H, m), 2.76 (1H, d, $J = 16.2$ Hz), 2.21 (1H, d, $J = 16.2$ Hz), 1.9-2.2 (2H, m), 1.0-1.8 (10H, m), 1.75 (3H, d, $J = 1.0$ Hz), 1.41 (3H, s), 1.34 (3H, s), 1.29 (3H, s), 1.19 (3H, s), 0.92 (3H, s); $^{13}C$-NMR (67.5 MHz, $CDCl_3$): $\delta = 204.3$, 145.1, 137.8, 105.6, 87.1, 58.9, 41.5, 39.8, 39.0, 38.0, 31.2, 29.7, 28.1, 26.81, 26.78, 26.4, 26.2, 23.6, 22.1, 21.9, 21.5, 20.8; IR (neat): $\tilde{\nu} = 2922, 1671\ cm^{-1}$; high-resolution MS (EI): calcd for $C_{22}H_{34}O_3$ 346.2508 ($M^+$), found 346.2493; NOEs: 19-Me↔H-2, H-2↔17-Me, 19-Me↔H-9/H-9'.

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# Cofactor-Assisted Self-Cleavage in DNA Libraries with a 3'-5'-Phosphoramidate Bond[**]

Jens Burmeister, Günter von Kiedrowski,[*] and Andrew D. Ellington

*Dedicated to Dr. Leslie E. Orgel on the occasion of his 70th birthday*

The technique of directed molecular evolution[1] is a powerful tool in the emerging field of evolutive biotechnology. In vitro selections have been carried out to isolate RNA aptamers directed against various molecular targets[2] and to develop artificial ribozymes with stunning catalytic properties.[3] Preliminary results with DNA indicate that artificial deoxyribozymes exhibiting interesting catalytic functions can be achieved as well.[4] Directed molecular evolution may also prove useful in the search for an exponential self-replicating system based on oligodeoxynucleotide analogs.[5] Our objective was to select a 5'-aminooligodeoxynucleotide that can catalyze the carbodiimide-dependent condensation of the trideoxynucleotides CCGp and pCGG to yield the hexameric 3'-5'-pyrophosphate CCGppCGG.[6] Such an aminooligodeoxynucleotide could act as a nucleophilic catalyst, that is, a leaving group, for phosphoryl transfer (Figure 1). Similar transphosphorylations involving phosphoramidates and pyrophosphates occur in reactions catalyzed by T7-DNA ligase.[7]

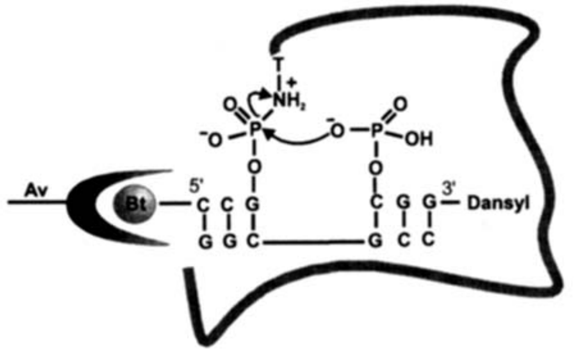

Figure 1. Schematic representation of the template-directed transphosphorylation reaction (Av = Avidine, Bt = Biotin).

To better understand the proposed transphosphorylation, we studied uncatalyzed reactions between N3-CCGpnT (**1**) and pCGG-dansyl (**2**) with HPLC (UV and fluorescence detection).[8] Even after long reaction times (up to two months) no fluorescent hexadeoxynucleotide N3-CCGppCGG-dansyl resulting from phosphoryl transfer could be detected. Hydrolysis of the 3'-5'-phosphoramidate bond (pn bond) was the only reaction observed, and the logarithm of the rate of hydrolysis is linearly dependent on the pH of the aqueous solvent. Between pH = 3 and 7,[9] the pseudo-first-order rate constants follow Equation (1).

$$\lg(k/h^{-1}) = 1.2 - 0.97 \times \mathrm{pH} \qquad (1)$$

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