MS m/e (rel int) 391 (M^+, 0.21), 376 (4), 291 (16), 251 (17), 250 (100), 208 (6), 168 (7), 149 (5), 125 (32). Anal. Calcd for $C_{21}H_{29}NO_4S$: C, 64.42; H, 7.46; N, 3.58; S, 8.19. Found: C, 64.42; H, 7.48; N, 3.48; S, 8.11.

Registry No. 1, 36526-15-5; 2, 110426-80-7; 2-d_n, 119039-24-6; 3, 119039-00-8; 4, 87504-85-6; 5, 77199-25-8; 6, 105970-70-5; 7, 119039-01-9; 8, 119039-02-0; 9, 119039-03-1; 9-d_n, 119039-25-7; 10, 119073-05-1; 11, 110426-81-8; 12, 119039-04-2; 13, 110426-82-9; 14, 119039-05-3; 15, 110426-83-0; 16, 110426-84-1; 17, 119039-06-4; 18, 105970-96-5; 19, 110426-85-2; 20, 119039-07-5; 21, 119039-08-6; 22, 119039-09-7; 23, 119073-06-2; 24, 119039-10-0; 25, 119073-07-3; *trans*-26, 119039-11-1; *cis*-26, 119039-15-5; 27, 119073-08-4; 28, 119039-12-2; 29, 99699-08-8; 30, 119039-13-3; 31, 105970-95-4; 32, 110426-86-3; 33, 119039-14-4; 37, 119039-16-6; 38, 119039-17-7; 39, 119070-24-5; 39 (sulfide), 119039-26-8; 42, 119039-18-8; 43, 119039-19-9; 43 (acid), 66241-77-8; 44, 119039-20-2; 44 (acid), 74903-61-0; 45, 119039-21-3; 46, 119039-22-4; 49, 119039-23-5; $H_2C{=}C(CH_3)CO_2C_6H_{11}$, 101-43-9; $H_2C{=}C(CH_3)COPh$, 2177-70-0; $H_2C{=}C(CH_3)CONPhMe$, 15796-89-1; $H_2C{=}C(CH_3)CO_2n$-Bu, 97-88-1; $H_2C{=}C(CH_3)CO_2Me$, 80-62-6; $H_2C{=}C(SiMe_3)CO_2Me$, 18269-31-3; $H_2C{=}C(CH_3)SO_2Ph$, 76380-14-8; $H_2C{=}CHCONPhMe$, 6273-94-5; $H_2C{=}C(CH_3)CN$, 126-98-7; $PhCH{=}C(CO_2Et)_2$, 5292-53-5; 2-(bromomethyl)acrylic acid, 72707-66-5; thiophenol, 108-98-5; sodium benzenesulfinate, 873-55-2; 2-cyclopenten-1-one, 930-30-3; 2-cyclohexen-1-one, 930-68-7; *N*-methylaniline, 100-61-8.

Supplementary Material Available: Experimental details for the syntheses of 3-9, 13, 14, 18-20, 22, 24, 26, 28, 30, 32, 37-39, 42-46, and 49 (21 pages). Ordering information is given on any current masthead page.

Crotofolane Diterpenoids from the African Shrub *Croton dichogamus* Pax.

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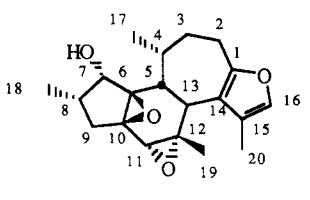
Two new crotofolane diterpenoids, crotoxides A (1) and B (2), have been isolated from the African shrub *Croton dichogamus*. The structure of crotoxide A (1) was determined by a combination of spectroscopic and single-crystal X-ray diffraction analyses. The proposed structure of crotoxide B (2) was based on spectroscopic comparison to crotoxide A (1).

Elephants in the Serengeti-Mara region of northern Tanzania and southern Kenya feed on a wide variety of trees and shrubs, but they show distinct preferences.[1] In particular, they prefer *Acacia* species such as *A. gerradii* Benth. while eating the *Croton dichogamus* Pax. to a lesser extent and another shrub *Euclea divenorum* Hiern. to an even lesser extent.[2] We have examined the chemical constituents of *C. dichogamus* leaves as part of an ongoing program aimed at identifying plant metabolites that might influence the elephants' browsing behavior. Our investigations have resulted in the isolation of two interesting new crotofolane diterpenoids, crotoxide A (1) and crotoxide B (2), whose structures we now report.



1 2

The dichloromethane-soluble portion of the methanol extract of air-dried *C. dichogamus* leaves was fractionated by silica gel flash and silica gel preparative TLC chromatographies to give crude samples of crotoxides A (1) and B (2). Final purification of each of the metabolites proved to be extremely difficult due to the presence of numerous minor but persistent contaminants. Mild hydrogenation of each of the crude samples substantially changed the polarity of the contaminants without altering the metabolites of interest, as shown by ^1H NMR and TLC analysis of the crude samples before and after hydrogenation. HPLC fractionation of each of the hydrogenated crude fractions gave pure samples of diterpenoids 1 and 2.

Crotoxide A (1), obtained as colorless needles (mp 149-152 °C) from hexane, gave a parent ion in the HREIMS at m/z 330.1837 Da (daltons), appropriate for a molecular formula of $C_{20}H_{26}O_4$ (ΔM + 0.6 mmu), requiring eight sites of unsaturation. The ^{13}C NMR spectrum of crotoxide A (Table II) showed well-resolved resonances for all 20 carbons, and an APT[3] experiment demonstrated that 25 of the protons were attached to carbon atoms. An IR band at 3477 cm^{-1} revealed that the remaining proton was part of an alcohol functionality.

Four deshielded carbon resonances (δ (C_6D_6) 118.9 (C), 121.6 (C), 137.2 (CH), and 150.5 (C); Table II) and a deshielded proton resonance (δ (C_6D_6) 6.92 br s; Table I) were assigned to an α,β,β'-trisubstituted furan fragment. A COSY experiment (C_6D_6) showed coupling between the furan proton (δ 6.92) and a set of methyl protons at δ 1.96 (d, J = 1 Hz), and irradiation of the methyl protons induced a NOE in the furan proton. The methyl residue, therefore, had to be attached to the β-carbon adjacent to

(1) For prior studies on this general topic, see: Sinclair, A. R. E.; Jogia, M. K.; Andersen, R. J. *J. Chem. Ecol.* **1988**, *14*, 1505.

(2) Dublin, H. T. Ph.D. Thesis. Decline of the Mara Woodlands: The Role of Fire and Elephants. Dept. of Zoology, University of British Columbia, 1986.

(3) Patt, S. L.; Shoolery, J. N. *J. Magn. Reson.* **1982**, *46*, 535.

0022-3263/89/1954-1654$01.50/0

Table I. ^{1}H NMR (400 MHz) Data for Crotoxides A (1) and B (2)[a]

proton on carbon no.	1[b]	1[c]	2[b]
2	2.90, m	2.75, m	2.85, m
	2.75, m	2.65, m	3.13, dd, J = 8, 15 Hz
3	2.0, m	1.58, m	4.48, dd, J = 8, 10 Hz
	1.75, m	1.75, m	
4	2.62, m	2.45, m	–
5	2.17, br d, J = 12 Hz	2.23, br d, J = 12 Hz	3.24, d, J = 12 Hz
7	4.23, dd, J = 6, 6 Hz	3.80, dd, J = 5, 5 Hz	5.56, d, J = 5 Hz
8	2.00, m	1.87, m	–
9	2.14, m	1.96, dd, J = 7, 13 Hz	2.48, dd, J = 8, 14 Hz
	1.65, dd, J = 10, 14 Hz	1.63, dd, J = 10, 13 Hz	1.67, dd, J = 10, 14 Hz
11	3.13, s	3.02, s	3.19, s
13	2.66, br d, J = 12 Hz	2.88, br d, J = 12 Hz	2.81, d, J = 12 Hz
16	7.06, br s	6.92, br s	7.02, br s
17	0.99, d, J = 6 Hz*[d]	1.03, d, J = 6 Hz	5.21, br s
			5.12, br s
18	0.98, d, J = 6 Hz*	0.64, d, J = 6 Hz	0.92, d, J = 6 Hz
19	1.06, s	1.02, s	1.12, s
20	1.98, d, J = 1 Hz	1.96, d, J = 1 Hz	1.96, d, J = 1 Hz
OAc	–	–	2.14, s

[a] Chemical shifts are listed in parts per million from internal TMS. [b] Recorded in $CDCl_3$. [c] Recorded in C_6D_6. [d] (*) assignments may be reversed.

Table II. ^{13}C NMR Data (75 MHz) for Crotoxide A (1)[a]

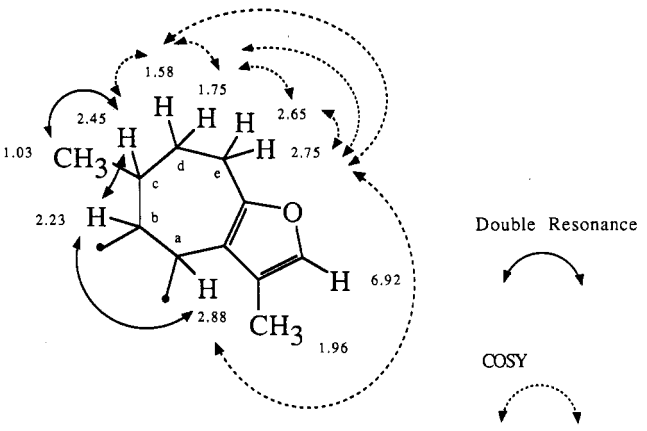
carbon no.	$CDCl_3$[b]	C_6D_6
1	150.2 (C)	150.5
2	22.7 (CH_2)	23.1
3	32.7 (CH_2)	33.0
4	29.5 (CH)	30.0
5	40.3 (CH)	40.8
6	72.3 (C)#[c]	72.4*[c]
7	75.0 (CH)	75.0
8	33.8 (CH)	34.2
9	33.6 (CH_2)	33.9
10	63.7 (C)#	63.8*
11	55.8 (CH)	56.3
12	64.2 (C)#	64.3*
13	44.8 (CH)	45.4
14	121.3 (C)&[c]	121.6&
15	118.1 (C)&	118.9&
16	136.6 (CH)	137.2
17	16.5 (CH_3)	16.8
18	12.0 (CH_3)	12.0
19	20.4 (CH_3)	20.6
20	8.9 (CH_3)	9.1

[a] Chemical shifts are reported in parts per million from internal TMS. [b] Proton attachments determined with APT. Assignments are based on HETCOR and SINEPT experiments. [c] (#,*,&) may be interchanged.

the unsubstituted α-carbon.

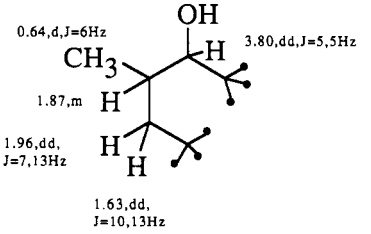
The lack of other olefinic or carbonyl resonances in the ^{13}C NMR spectrum of crotoxide A (Table II) indicated that rings had to account for the remaining five sites of unsaturation in the molecule. Carbon resonances at δ 56.3 (CH), 64.3 (C), 63.8 (C), and 72.4 (C) were tentatively assigned to trisubstituted and tetrasubstituted epoxide functionalities. A resonance at δ 3.02 (s) in the ^{1}H NMR spectrum of 1 was assigned to the lone epoxide methine proton. Irradiation of the proton singlet at δ 3.02 induced a strong NOE in a methyl resonance at δ 1.02 (s), suggesting that the trisubstituted epoxide had a methyl substituent cis to the methine proton. The alcohol, furan, and epoxide functionalities accounted for all the heteroatoms in crotoxide A. Therefore, three carbocyclic rings had to be incorporated into the structure to satisfy the unsaturation number.

^{1}H NMR experiments facilitated the identification of a seven-membered carbocyclic ring fused to the furan ring as shown in fragment A. Irradiation of the furan methyl protons at δ 1.96 induced a strong NOE in a methine proton at δ 2.88 (br d, J = 12 Hz), suggesting that the methine carbon was attached to the second β-carbon of the trisubstituted furan. Irradiation of the methine proton



Fragment A

(δ 2.88), in a SINEPT[4] experiment optimized for polarization transfer through a ^{13}C/^{1}H coupling constant of 7 Hz, showed transfer to both of the β-carbons of the furan ring (i.e., δ 118.9, 121.6), in agreement with the proposed connectivity. Double-resonance and COSY experiments established the connectivity from the methine at δ 2.88 around the ring to the geminal methylene protons resonating at δ 2.65 and 2.75, and they also fixed the position of the methyl substituent as illustrated in fragment A. The chemical shifts of the methylene protons on carbon e in fragment A (δ 2.65 and 2.75) were consistent with the attachment of this carbon to the substituted α position of the furan. Support for this connectivity came from a SINEPT experiment in which irradiation of the methylene proton at δ 2.65 showed polarization transfer to the furan carbons at δ 150.5 (α) and 121.6 (β), and from the observation in the COSY experiment of a homoallylic coupling between the methylene proton at δ 2.75 (H_e) and the methine proton at δ 2.88 (H_a). The remaining atoms of crotoxide A could be accounted for by the four-carbon fragment B, which was routinely identified from double-resonance and COSY experiments.



Fragment B

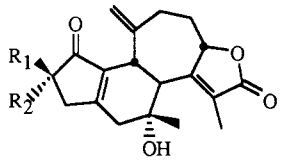
Previous chemical studies of *Croton corylifolius*,[5,6] a Jamaican relative of *C. dichogamus*, resulted in the dis-

(4) Bax, A. *J. Magn. Reson.* **1984**, *57*, 314.
(5) Chan, W. R.; Prince, E. C.; Manchand, P. S.; Springer, J. P.; Clardy, J. *J. Am. Chem. Soc.* **1975**, *97*, 4437.
(6) Burke, B. A.; Chan, W. R.; Pascoe, K. O.; Blount, J. F.; Manchand, P. S. *Tetrahedron Lett.* **1979**, 3345.

Table III. NOE Results for Crotoxide A (1) (400 MHz, C_6D_6)

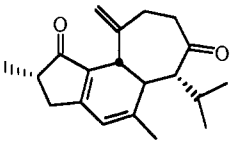
proton irradiated	NOE observed
1.02 (H19)	3.02 (H11), 1.96 (H20)
1.63 (H9a)	1.96 (H9b)
1.96 (H20)	6.92 (H16), 2.88 (H13)
2.23 (H5)	2.75 (H2a)
2.45 (H4)	2.23 (H5), 3.80 (H7)
3.02 (H11)	1.02 (H19)

covery of crotofolins A (3), B(4), C(5), and E(6), a family of diterpenoids having the crotofolane carbon skeleton.



3 R_1 = OH, R_2 = CH_3

4 R_1 = CH_3, R_2 = OH



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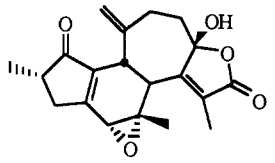

6

All of the identified structural fragments and observed spectroscopic features of crotoxide A could be readily accommodated by the crotofolane diterpenoid structure 1. NOE experiments (Table III) allowed a partial assignment of the relative stereochemistry of crotoxide A; however, the configurations at C6, C7, C8, and C10 remained undetermined from the NMR experiments. In order to complete the stereochemical assignment and to provide definitive proof of the constitution, the structure of crotoxide A (1) was determined by single-crystal X-ray diffraction analysis.

A computer-generated perspective drawing of the final X-ray model is given in Figure 1. Only the relative stereochemistry was determined, and the absolute configuration shown was arbitrarily chosen to agree with earlier work. The epoxide at the C6, C10 position is on the top face of the molecule, while the hydroxy at C7 and the methyl at C8 are on the bottom face. With the structure of crotoxide A securely established as 1, we turned our attention to crotoxide B (2).

Crotoxide B (2), isolated in trace amounts as a very unstable white amorphous powder, gave a parent ion at m/z 387 Da in the CIMS and at 386.1742 Da in the EIHRMS, appropriate for a molecular formula of $C_{22}H_{26}O_6$ (ΔM + 1.3 mmu). The small quantity and relative instability of crotoxide B made it extremely difficult to acquire high-quality NMR data for the compound. Only samples fresh off the HPLC gave acceptable spectra, while all other samples showed signals due to decomposition products. In spite of this difficulty, the similarity between the ^1H NMR data for crotoxide B (2) and that exhibited by crotoxide A (1) (Table I) implied that the two metabolites were closely related, allowing us to make a structural assignment.

Analysis of the differences in the ^1H NMR spectra of the two compounds led to the identification of the new functionalities in crotoxide B (2). One of the methyl doublets at δ 0.98 and 0.99 ($CDCl_3$: C17 and C18) in the spectrum of crotoxide A (1) was absent in the spectrum

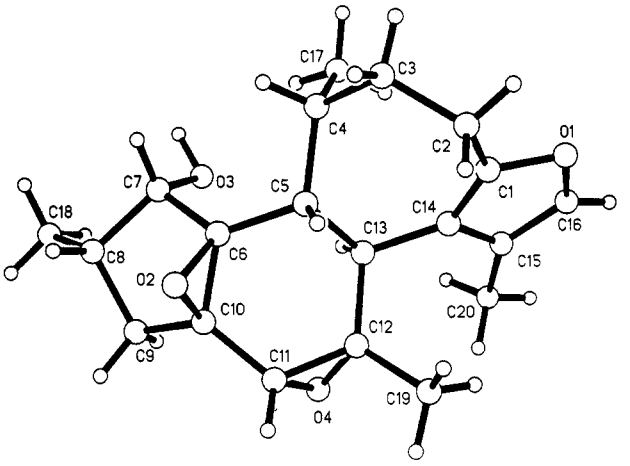

Figure 1. A computer-generated perspective drawing of the final X-ray model of crotoxide A (1). No absolute configuration is implied.

of crotoxide B (2) (Table I). A pair of olefinic proton resonances at δ 5.11 (br s) and 5.21 (br s) in the spectrum of 2 indicated that either the C17 or C18 methyl appendage in crotoxide B was present as an exocyclic methylene functionality. The IR spectrum of crotoxide B showed absorption bands at 3477 and 1742 cm^{-1}, assigned to OH and ester carbonyl stretching vibrations. A methyl singlet at δ 2.14 in the ^1H NMR spectrum of 2 identified the ester functionality as an acetate. Deshielded resonances at δ 4.48 (dd, J = 8, 10 Hz) and 5.56 (d, J = 5 Hz) were assigned to protons attached to methine carbons bearing the alcohol and acetoxy functionalities, respectively.

The multiplicity of the resonance at δ 4.48 (dd, J = 8, 10 Hz) required that the methine proton have two vicinal neighbors. Similarly, the multiplicity of the resonance at δ 5.56 (d, J = 5 Hz) required that the second deshielded methine proton have only one vicinal neighbor. Irradiation of the methine resonance at δ 4.48 induced a NOE in the olefinic methylene resonance at δ 5.12 while irradiation of the methine resonance at δ 5.56 induced a NOE in the other olefinic methylene proton at δ 5.21. The NOE results demonstrated that there was close a spatial proximity between the two deshielded methine protons and the olefinic methylene functionality. The proposed structure 2 for crotoxide B is consistent with all the above observations. Placement of the acetoxy functionality at C7 and the alcohol functionality at C3 in crotoxide B (2) was consistent with the observed downfield shift of the C7 methine resonance in the ^1H NMR spectrum of 2 (δ 5.56) compared to its chemical shift in crotoxide A (1) (δ 4.23). The relative stereochemistry of crotoxide B (2) was not readily determined by NMR on our sample; however, we have assumed that the relative configurations at C5, C6, C7, C8, C10, C11, and C13 are the same in both crotoxides A and B, as shown.

C. dichogamus is only the second plant known to contain crotofolane diterpenoids. Crotoxides A (1) and B (2) differ most notably from the crotofolins (3–6) isolated from *C. corylifolius* by having a furan instead of a butenolide ring and by the presence of the cyclohexane bis-epoxide substructure.

Experimental Section

NMR spectra were recorded on Varian XL 300 and Bruker WH 400 spectrometers. Tetramethylsilane was used as an internal standard. Low-resolution mass spectra were recorded on an AEI MS 902 spectrometer, and high-resolution mass spectra were recorded on an AEI MS 50 spectrometer. Infrared spectra were recorded on a Perkin-Elmer 1710 Fourier transform spectrometer.

Merck silica gel, 230–400 mesh, was used for flash chromatography, and Whatman Magnum-9 Partisil-10 and ODS-3 columns were used for preparative HPLC.

Isolation and Extraction. Fresh leaves of *C. dichogamus* were collected in Kenya in mid-1987 (a voucher sample has been deposited at the herbarium in the Botany Dept., UBC). The air-dried leaves (225 g) were soaked in methanol (500 mL) overnight. The methanol extract was concentrated in vacuo to a gum, water was added, and the resulting suspension was exhaustively extracted with CH_2Cl_2. Evaporation of the combined organic extracts in vacuo gave a residue, which was fractionated via silica gel flash chromatography (step gradient: CH_2Cl_2 to EtOAc) to give crude crotoxides A (1) and B (2).

Crotoxide A (1). The flash fractions containing crude crotoxide A (1) were combined and further purified by silica gel preparative TLC (2:1 CH_2Cl_2/EtOAc). The preparative TLC fraction containing crotoxide A was dissolved in methanol (5 mL), palladium on charcoal was added (20 mg), and the suspension was stirred at room temperature under 1 atm of hydrogen for 2 days. Filtration of the reaction mixture, followed by vacuum evaporation of the filtrate, gave an oily residue, which was fractionated on preparative silica gel HPLC (9:1 CH_2Cl_2/EtOAc) to give pure crotoxide A (1) (yield 0.005% dry wt.): colorless needles (hexane), mp 149–152 °C; $[\alpha]^{25}_D$ +113° ($CHCl_3$, *c* 0.2); IR ($CHCl_3$) 3477 cm^{-1}; ^1H NMR see Table I; ^{13}C NMR see Table II; HREIMS M^+ 330.1837 ($C_{20}H_{26}O_4$) (ΔM + 0.6 mmu); LRMS *m/z* (relative intensity) 330 (62), 315 (20), 297 (9), 189 (42), 43 (100).

Crotoxide B (2). Crotoxide B (2) was partially purified by using the same flash, preparative TLC, and hydrogenation procedures described above for crotoxide A (1). Preparative reverse-phase HPLC (1:10 H_2O/CH_3CN) of the hydrogenation mixture residue gave pure crotoxide B (2) as an unstable white powder. 2: IR ($CHCl_3$) 3477, 1742, 1455, 1235 cm^{-1}; ^1H NMR see Table I; HREIMS M^+ 386.1742 ($C_{22}H_{26}O_6$) (ΔM + 1.3 mmu).

X-ray Analysis of Crotoxide A (1). The crystals grown from hexane were suitable for single-crystal X-ray analysis, and a specimen roughly 0.3 × 0.3 × 0.2 was mounted on a glass fiber. From preliminary X-ray photographs, the crystals were unambiguously assigned to space group $P2_12_12_1$ with cell constants of a = 6.402 (3) Å, b = 15.495 (6) Å, and c = 19.619 (6) Å determined from a least-squares fit of 25 2θ values. One molecule of composition $C_{20}H_{26}O_4$ formed the asymmetric unit giving a crystal density of 1.25 g/cm^3. All unique diffraction maxima with $2\theta \leq 114°$ were collected by using variable-width θ–2θ scans. Of the 1385 symmetry-unique reflections, 1293 (93%) were judged observed ($|F_o| > 3\sigma(F_o)$) after correction for Lorentz, background, and polarization effects. A phasing model was easily found by using the SHELX library of programs, and full-matrix least-squares refinements with anisotropic non-hydrogen atoms and riding hydrogen atoms smoothly converged to a conventional crystallographic residual of 0.050 for the observed reflections. Additional crystallographic details are available and are described in the paragraph entitled "Supplementary Material Available" at the end of this paper.

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Supplementary Material Available: Tables 1–5 of fractional coordinates, thermal parameters, bond distances, and bond angles from the X-ray analysis of crotoxide A (1) (5 pages). Ordering information is given on any current masthead page.

Synthesis of Phosphate-Methylated DNA Fragments Using 9-Fluorenylmethoxycarbonyl as Transient Base Protecting Group

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Synthesis of the phosphate-methylated DNA dinucleotides d(CpG) (4), d(GpC) (5), d(ApC) (6), d(ApT) (7), d(ApA) (8), and d(CpC) (9) is described. The 9-fluorenylmethoxycarbonyl (Fmoc) group was used for the protection of the amino groups of the bases A, C, and G during the synthesis. In contrast to routinely used benzoyl or isobutyryl groups, Fmoc could be easily removed without cleavage of the methyl phosphotriester group. Initially, the systems 4–9 were obtained as mixtures of R_p and S_p diastereoisomers. These were separated on a milligram scale with reversed-phase HPLC. Use of Fmoc is regarded as the method of choice for the preparation of phosphate-methylated DNA fragments. Fmoc synthesis of longer phosphate-methylated DNA's will open the possibility to evaluate the utility of these neutral DNA analogues as antisense matagens for inhibition of DNA replication and transcription in vitro and in vivo.

Introduction

A survey of the current literature shows that there is a growing interest in nucleic acid analogues possessing modified internucleoside linkages. Two types of modifications can be distinguished: (i) oligonucleotide alkyl phosphotriesters[1] and (ii) oligonucleotide methyl phosphonates.[2] Both modifications correspond with a neutral backbone structure, which leads to interesting chemical and biological properties. These include formation of stable hydrogen-bonded complexes with complementary

Table I. Optimal Parameters of the Reversed-Phase HPLC Separations

compd	modifier	%	pH	K'_{R_p}	α
4	acetonitrile	6	7.1	8.6	1.14
5	acetonitrile	8	7.1	8.5	1.12
6	methanol	25	5.2	5.8	1.08
7	methanol	30	4.2	8.2	1.19
8	acetonitrile	17	5.0	8.0	1.10
9	acetonitrile	13	3.5	2.6	1.08

[†] Eindhoven University of Technology.
[‡] DSM Research.

0022-3263/89/1954-1657$01.50/0