olefination.[26] Attempted radical cyclization of **10**, using $NaBH_4$ or Bu_3SnH (Scheme III), gave only the reduced product **12** (in 81% and 87% yield, respectively).[27,28] However, as with the aldehyde **3**, copper reagents proved more rewarding. First, organomercurial **10** was methylated with MeCu or Me_3Al to give **13** (in 91% and 95% yield, respectively.)[29] Although in this instance MeLi produced a complex mixture on reaction with **13**, Me_2CuLi afforded the desired cyclobutane derivative **15** (40%).[30] Alternatively, **15** was obtained in much higher isolated yield (75%) in one pot from **10** on reaction with Me_2CuLi.[31] This behavior suggests that the actual reactive species **14** involves copper. Although the structure of **14** is unknown, it seems reasonable to assume[20] that M = $CuLiCH_3$ or $CuHgLiCH_3$ and that the more suitably positioned C(4) in the complex **14** adds across the double bond in preference to the CH_3 group.

In conclusion, we have achieved a unique, regio- and stereoselective opening of a cyclopropane ring by Hg(II) followed by a skeletal rearrangement, generating a "5,5" system (**1** → **3**). As a result of specific transmetalations (with Li or Cu) we have been able to effect a highly stereoselective, intramolecular addition to a carbonyl group and/or across a conjugated double bond, and so construct a "5,5,4" tricyclic system (**3** → **9** and **10** → **15**). These transformations represent a novel methodology for cyclobutane annulation that may be of general use in view of the rather limited number of alternative approaches[32] and of the failure of radical reactions.[33] Alternatively, we believe that the strategy employing organomercurials, which can be generated by a number of stereoselective routes,[7f] may result in the development of a general method for the stereoselective construction of rings of various size, and for intermolecular coupling as well.

Acknowledgment. We thank Profs. M. Nilsson and J.-E. Bäckvall, and Dr. T. Olsson for stimulating discussions and Drs. G. Griffith and A. Gogoll for obtaining the NMR spectra. We also thank Merck Sharp and Dohme and the University of Leicester for financial support to J.Š.

Supplementary Material Available: Representative experimental procedures and characterization data for new compounds (8 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

(25) IR: $\nu_{C=O}$ = 1702 cm^{-1}. ^1H NMR: 5.92 (d, J = 16.0 Hz, 1 H, CH=C*H*CO_2Et), 7.06 (d, 1 H, J = 16.0 Hz, C*H*=$CHCO_2Et$) ppm. ^{13}C NMR: 119.57 (d), 151.98 (d), 166.46 (s) ppm.

(26) Although the reaction was rather slow [$(EtO)_2P(O)CH_2CO_2Et$, BuLi, THF, reflux for 12 h] due to steric hindrance, the yield of **10** was very good (73%). To our knowledge, this is the first successful Wittig-type olefination in the presence of an HgBr group in the substrate molecule. No reaction of aldehyde **3** was observed with Wittig reagents Ph_3P=CHR or with Ph_3As=CH_2, presumably due to the preferential coordination of Hg to P or As.

(27) Analogous radical cyclization of an organomercurial intermediate has been successfully employed to construct a five-membered ring.[18]

(28) Attempted intramolecular Heck coupling, using various Pd(II)-reagents, resulted solely in β-elimination (to give a product with an endocyclic double bond in 93% yield). This is in sharp contrast to the analogous cyclization that occurs readily to produce five-membered rings.[18]

(29) ^1H NMR: 0.25 (s, 3 H, CH_3Hg), 5.84 (d, 1 H, J = 16.0 Hz, CH=C*H*CO_2Et), 7.15 (d, 1 H, J = 16.0 Hz, C*H*=$CHCO_2Et$) ppm. ^{13}C NMR: 20.92 (CH_3Hg), 118.03 (d), 154.73 (d), 166.89 (s) ppm.

(30) IR: $\nu_{C=O}$ = 1728 cm^{-1}. ^{13}C NMR: 173.20 (s) ppm.

(31) Cyclobutane derivative **15** can also be obtained in high yield (92%) from **13** on reaction with Me_3Al/BuLi. We believe that, in this instance, the Lewis acid (Me_3Al) accelerates the conjugate addition, as in its absence only a complex mixture was produced.

(32) For methods of construction of four-membered rings, see: (a) Trost, B. M., Fleming, I., Eds. *Comprehensive Organic Synthesis*; Pergamon: Oxford, 1991; Vol. 1, p 843; Vol. 3, pp 588 and 620; Vol. 5, pp 63, 123, and 899. (b) Kočovský, P.; Tureček, F.; Hájíček, J. *Synthesis of Natural Products: Problems of Stereoselectivity*; CRC: Boca Raton, FL, 1986; Vol. 1, pp 39, 96, and 145. For a recent enantioselective approach, see: (c) Nemoto, H.; Ishibashi, H.; Nagamochi, M.; Fukumoto, K. *J. Org. Chem.* **1992**, *57*, 1707.

(33) Recently, an ionic, intramolecular addition across a conjugated double bond to form a four-membered ring, has been reported: Cooke, M. P., Jr. *J. Org. Chem.* **1992**, *57*, 1495.

Novel, Enantioselective Lactone Construction. First Synthesis of Methylenolactocin, Antitumor Antibiotic from *Penicillium* sp.

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Summary: The first synthesis of (−)-methylenolactocin, which illustrates a novel approach to enantiopure γ-butyrolactones and serves to confirm the structure and establish the absolute stereochemistry of the natural product, is reported.

α-Methylene-γ-butyrolactones,[1] ubiquitous, biologically significant compounds, represent approximately 10% of all structurally elucidated natural products.[1e] Enantioselective entry to the γ-butyrolactones, the structural units from which the α-methylene analogues are generally derived,[1b,e,f] is thus methodologically important and has, in recent years, been addressed with varying degrees of success in a number of laboratories.[2]

(1) For reviews on the occurrence, biological properties, and synthesis of α-methylene-γ-butyrolactones, see: (a) Yoshioka, H.; Mabry, T. J.; Timmermann, B. N. *Sesquiterpene Lactones*; University of Tokyo Press: Tokyo, 1973. (b) Grieco, P. A. *Synthesis* **1975**, 67–82. (c) Heywood, H.; Harborne, J. B.; Turner, B. L. *The Biology and Chemistry of the Compositae*; Academic Press: London, 1977; Vols. 1 and 2. (d) Fischer, N. H.; Oliver, E. J.; Fischer, H. D. In *Progress in the Chemistry of Organic Natural Products*; Herz, W., Grisebach, H., Kirby, G. W., Eds.; Springer-Verlag: New York, 1979; Vol. 38, Chapter 2. (e) Hoffmann, H. M. R.; Rabe, J. *Angew. Chem., Int. Ed. Engl.* **1985**, *24*, 94–110. (f) Petragnani, N.; Ferraz, H. M. C.; Silva, G. V. J. *Synthesis* **1986**, 157–183.

(2) For recent approaches, see: Mukaiyama, T.; Suzuki, K. *Chem. Lett.* **1980**, 255–256. Takano, S.; Imamura, Y.; Ogasawara, K. *Tetrahedron Lett.* **1981**, *22*, 4479–4482. Toda, F.; Tanaka, K.; Omata, T.; Nakamura, K.; Oshima, T. *J. Am. Chem. Soc.* **1983**, *105*, 5151–5152. Marino, J. P.; Perez, A. D. *Ibid.* **1984**, *106*, 7643–7644. Kosugi, H.; Konta, H.; Uda, H. *J. Chem. Soc., Chem. Commun.* **1985**, 211–213. Thijs, L.; Waanders, P. P.; Stokkingreef, E. H. M.; Zwanenburg, B. *Recl. Trav. Chim. Pays-Bas* **1986**, *105*, 332–337. Marino, J. P.; Laborde, E.; Paley, R. S. *J. Am. Chem. Soc.* **1988**, *110*, 966–968. Salaun, J.; Karkour, B. *Tetrahedron Lett.* **1988**, *29*, 1537–1540. Hoppe, D.; Zschage, O. *Angew. Chem., Int. Ed. Engl.* **1989**, *28*, 69–71. Chong, J. M.; Mar, E. K. *Tetrahedron Lett.* **1990**, *31*, 1981–1984. Ohkuma, T.; Kitamura, M.; Noyori, R. *Ibid.* **1990**, *31*, 5509–5512. Kitamura, M.; Tokunaga, M.; Ohkuma, T.; Noyori, R. *Ibid.* **1991**, *32*, 4163–4166. Doyle, M. P.; van Oeveren, A.; Westrum, L. J.; Protopopova, M. N.; Clayton, T. W., Jr. *J. Am. Chem. Soc.* **1991**, *113*, 8982–8984.

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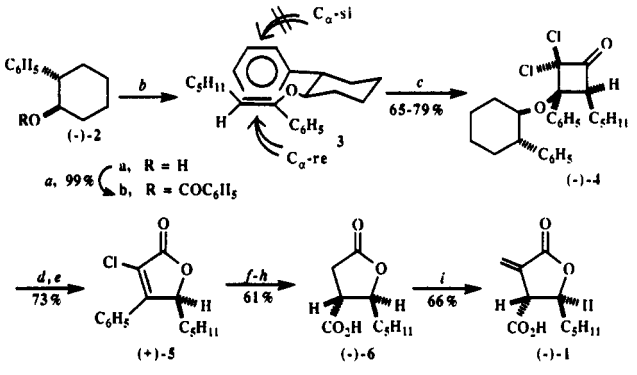
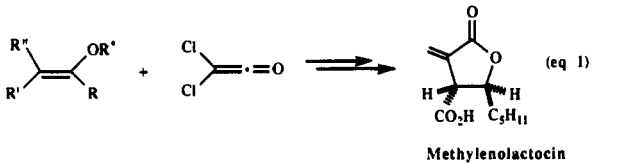
Scheme I



[a] C_6H_5COCl, DMAP, C_5H_5N, 20 °C, 12 h. [b] $C_6H_{12}Br_2$, Zn, $TiCl_4$, TMEDA, THF–CH_2Cl_2 (3:1), 0 → 20 °C, 3 h. [c] Cl_3CCOCl, Zn–Cu, $(C_2H_5)_2O$, 20 °C, 6 h. [d] MCPBA, $NaHCO_3$, CH_2Cl_2, 20 °C, 11 h. [e] $Cr(ClO_4)_2$, acetone, 0 °C, 1 h. [f] H_2, 10% Pd–C, CH_3CO_2Na, CH_3OH, 20 °C, 20 h. [g] $RuCl_3$, $NaIO_4$, CCl_4–CH_3CN–H_2O (1:1:1.5), 38 °C, 72 h. [h] CH_2N_2, $(C_2H_5)_2O$; DBU, CH_2Cl_2, 20 °C, 72 h; 6 N HCl, dioxane, reflux, 2 h. [i] $MgOCO_2CH_3$, DMF, 135 °C, 69 h; aqueous HCHO, $C_6H_5NHCH_3$, CH_3CO_2Na, CH_3CO_3H, 20 °C, 2 h.

In this communication we report the first synthesis of (−)-methylenolactocin, a densely functionalized and isomerization-prone antitumor antibiotic isolated from the culture filtrate of *Penicillium* sp.[3] This work (1) illustrates a novel and potentially general approach to enantiopure γ-butyrolactones, (2) exemplifies a significantly improved procedure for effecting their conversion to the important α-methylene derivatives, and (3) confirms the structure and establishes the absolute stereochemistry of the natural product. Our approach is based on π-face differentiation in chiral olefin–ketene [2 + 2]-cycloaddition (eq 1),[4] which represents a new strategy for enantioselective lactone construction.



(eq 1)

Methylenolactocin

Easily available (1*R*,2*S*)-(−)-2-phenylcyclohexanol[5] (Scheme I) was converted conventionally in 99% yield to the corresponding benzoate (−)-**2b**,[6] which in turn was added simultaneously with 1,1-dibromohexane to premixed Zn–$TiCl_4$–TMEDA in CH_2Cl_2–THF to produce stereoselectively the *Z*-enol ether **3** (*Z*:*E* ca. 9:1 by ^1H NMR) in nearly quantitative yield.[7]

It was expected on steric grounds that the reactive conformation of this enol ether on cycloaddition with dichloroketene would be the depicted *s*-trans,[8] in which the C_α-*re* face is effectively open to attack, while the C_α-*si* face is placed so as to be screened by the neighboring C-2 phenyl. In the event, the enol ether on exposure to dichloroketene[9] did indeed experience substantial π-face discrimination and yielded highly diastereoselectively the crystalline cyclobutanone adduct (−)-**4**[6] in up to 79% yield after recrystallization.[10,11]

Baeyer–Villiger ring expansion of this α,α-dichlorocyclobutanone furnished with total regioselectivity the expected[12] α,α-dichloro-γ-butyrolactone, which on reaction with chromous perchlorate[13] in acetone underwent smooth conversion to provide the α-chlorobutenolide (+)-**5**[6] in 73% yield (with concomitant recovery of the intact chiral auxiliary). On reduction with H_2/Pd–C and then oxidation with $RuCl_3$–$NaIO_4$,[14] (+)-**5** gave a mixture of β-carboxy-γ-butyrolactones, which could be conveniently equilibrated with DBU (methyl esters) to give in 61% overall yield the enantiopure trans lactone (−)-**6**.[6]

In view of the propensity, in the presence of base, of molecules similar to **6** to suffer ring cleavage[15] and that of protolichesterinic acid, a homologue of methylenolactocin, to undergo double bond isomerization,[15a,16] the introduction of the requisite methylene was a source of considerable concern. After numerous, totally unrewarding attempts to effect this conversion,[17] it was discovered, much to our delight, that modification of the decarboxylative methylenation procedure developed by Johnson and co-workers[15b] provided a highly effective solution. Treatment of (−)-**6** with Stiles reagent[18] and then a buffered solution of aqueous formaldehyde and *N*-methyl-

(3) Park, B. K.; Nakagawa, M.; Hirota, A.; Nakayama, M. *J. Antibiot.* **1988**, *41*, 751–758. Nakayama, M.; Nakagawa, S.; Boku, T.; Hirota, A.; Shima, S.; Nakanishi, O.; Yamada, Y. *Jpn. Kokai Tokkyo Koho* **1989**, *1*, 16,776; *Chem. Abstr.* **1990**, *112*, 34404f.

(4) See: Greene, A. E.; Charbonnier, F. *Tetrahedron Lett.* **1985**, *26*, 5525–5528. Greene, A. E.; Charbonnier, F.; Luche, M.-J.; Moyano, A. *J. Am. Chem. Soc.* **1987**, *109*, 4752–4753. Cf. Fráter, G.; Müller, U.; Günther, W. *Helv. Chim. Acta* **1986**, *69*, 1858–1861.

(5) $[\alpha]^{21}_D$ −58.9° (*c* 10, CH_3OH). See: Whitesell, J. K.; Chen, H. H.; Lawrence, R. M. *J. Org. Chem.* **1985**, *50*, 4663–4664. Whitesell, J. K.; Lawrence, R. M. *Chimica* **1986**, *40*, 318–321. Schwartz, A.; Madan, P.; Whitesell, J. K.; Lawrence, R. M. *Org. Synth.* **1990**, *69*, 1–9.

(6) Spectroscopic (NMR, IR, MS) data are in full accord with the proposed structure. Satisfactory combustion and/or high resolution mass spectral data have been obtained for this compound. The stated yield is for the purified, chromatographically homogeneous substance. (−)-**2b**: mp 73–75 °C, $[\alpha]^{21}_D$ −129° (*c* 2.0, $CHCl_3$). (−)-**4**: mp 97–100 °C, $[\alpha]^{21}_D$ −32° (*c* 1.3, $CHCl_3$). (+)-**5**: 33–34 °C, $[\alpha]^{20}_D$ +152° (*c* 1.2, $CHCl_3$). (−)-**6**: mp 105–107 °C dec, $[\alpha]^{21}_D$ −54° (*c* 0.5, $CHCl_3$). (−)-**1**: mp 82–84 °C, $[\alpha]^{26}_D$ −6.7° (*c* 0.5, CH_3OH).

(7) Okazoe, T.; Takai, K.; Oshima, K.; Utimoto, K. *J. Org. Chem.* **1987**, *52*, 4410–4412. The vinyl proton of the *Z* isomer resonates at 4.97 ppm (t, *J* = 7.1 Hz) and that of the *E* isomer at 4.82 ppm (t, *J* = 7.6 Hz). 1,1-Dibromohexane was prepared by a known procedure: Villieras, J.; Bacquet, C.; Normant, J.-F. *Bull. Soc. Chim. Fr.* **1975**, 1797–1802.

(8) In general, an *s*-trans or nearly *s*-trans conformation is assumed by *cis*-alkenyl ethers. See: Fischer, P. In *Chemistry of Ethers, Crown Ethers, Hydroxyl Groups, and Their Sulphur Analogues*; Patai, S., Ed.; John Wiley and Sons: New York, 1980; Vol. 2, Chapter 17. The depicted *s*-trans conformation, in addition to suffering fewer steric constraints, may benefit from favorable π–π interaction. See: Whitesell, J. K.; Lawrence, R. M.; Chen, H. H. *J. Org. Chem.* **1986**, *51*, 4779–4784.

(9) Generated in situ. See: Krepski, L. R.; Hassner, A. *J. Org. Chem.* **1978**, *43*, 3173–3179.

(10) NMR examination of the crude product, as well as the mother liquor, revealed the presence of only very minor amounts of several possible diastereoisomeric compounds (unstable to chromatography). By using the most significant of these as a lower limit, we were able to determine the level of diastereoselection to be ≥9:1.

(11) In that electron-withdrawing groups are known to deactivate ketenophiles, the phenyl was chosen as a latent carbalkoxyl group. It was anticipated that the presence of this phenyl would facilitate not only the cycloaddition but also the subsequent elimination of the chiral auxiliary.

(12) See: Belluš, D.; Ernst, B. *Angew. Chem., Int. Ed. Engl.* **1988**, *27*, 797–827.

(13) Kochi, J. K.; Singleton, D. M. *J. Am. Chem. Soc.* **1968**, *90*, 1582–1589. Wade, R. S.; Castro, C. E. *Org. Synth.* **1972**, *52*, 62–66.

(14) Carlsen, P. H. J.; Katsuki, T.; Martin, V. S.; Sharpless, K. B. *J. Org. Chem.* **1981**, *46*, 3936–3938. See also: Nunez, M. T.; Martin, V. S. *Ibid.* **1990**, *55*, 1928–1932.

(15) (a) van Tamelen, E. E.; Bach, S. R. *J. Am. Chem. Soc.* **1958**, *80*, 3079–3086. (b) Martin, J.; Watts, P. C.; Johnson, F. *J. Org. Chem.* **1974**, *39*, 1676–1681.

(16) Cavallito, C. J.; Fruehauf, McK. D.; Bailey, J. H. *J. Am. Chem. Soc.* **1948**, *70*, 3724–3726. Carlson, R. M.; Oyler, A. R. *J. Org. Chem.* **1976**, *41*, 4065–4069.

(17) Reagents examined in this context include: Eschenmoser's salt (Danishefsky, S.; Kitahara, T.; McKee, R.; Schuda, P. F. *J. Am. Chem. Soc.* **1976**, *98*, 6715–6717. Roberts, J. L.; Borromeo, P. S.; Poulter, C. D. *Tetrahedron Lett.* **1977**, 1621–1624); HCHO (Grieco, P.; Hiroi, K. *J. Chem. Soc., Chem. Commun.* **1972**, 1317–1318); Brederick's reagent (Danishefsky, S.; Hirama, M.; Gombatz, K.; Harayama, T.; Berman, E.; Schuda, P. *J. Am. Chem. Soc.* **1979**, *101*, 7020–7031).

(18) Stiles, M. *J. Am. Chem. Soc.* **1959**, *81*, 2598–2599. Finkbeiner, H. L.; Stiles, M. *Ibid.* **1963**, *85*, 616–622.

aniline[19,20] afforded in 66% yield synthetically derived (−)-methylenolactocin (mp 82–84 °C; $[\alpha]^{26}_D$ −6.7° (*c* 0.5, CH_3OH)), spectroscopically and chromatographically indistinguishable from the naturally derived substance (mp 82–84 °C; mmp 82–84 °C; $[\alpha]^{26}_D$ −6.8° (*c* 0.5, CH_3OH)).[21,22]

In summary, the feasibility of using chiral olefin diastereofacial differentiation for enantioselective lactone construction has been demonstrated through a high-yield (>20% overall) preparation of enantiopure, natural methylenolactocin. Application of this methodology to the synthesis of congeneric natural products[25] is planned.

Acknowledgment. We thank Prof. J. Lhomme for his interest in our work and Prof. B. K. Park for a sample of natural methylenolactocin. Financial support from the CNRS (URA 332) and fellowship awards from the CNPq to M.B.M.A. and M.M.M. are gratefully acknowledged.

Registry No. (−)-1, 112923-53-2; (−)-**2a**, 98919-68-7; (−)-**2b**, 129098-11-9; **3**, 142188-46-3; (−)-**4**, 142188-47-4; (+)-**5**, 142188-49-6; **6** diacid derivative, 142188-52-1; (−)-**6**, 142188-51-0; (−)-**6** methyl ester, 142235-91-4; 1,1-dibromohexane, 58133-26-9; trichloroacetyl chloride, 76-02-8; (4*R*,5*S*)-3,3-dichloro-5-pentyl-4-phenyl-4-[((1*R*,2*S*)-2-phenylcyclohexyl)oxy]dihydro-2(3*H*)-furanone, 142188-48-5; (4*R*,5*S*)-5-pentyl-4-phenyldihydro-2(3*H*)-furanone, 142188-50-9; (4*S*,5*S*)-5-pentyl-4-phenyldihydro-2(3*H*)-furanone, 142188-53-2.

Supplementary Material Available: Complete experimental procedures with spectral and analytical data for the preparation of compounds 1–6 (5 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the Journal, and can be ordered from the ACS; see any current masthead page for ordering information.

(19) Cf. Gras, J.-L. *Tetrahedron Lett.* **1978**, 2111–2114.
(20) Preliminary results indicate that this modification represents a general improvement over the original procedure(s)[15] in terms of both mildness and yield. The procedure used by Johnson and co-workers for the preparation of (±)-protolichesterinic acid ($MgOCO_2CH_3$; HCHO, $(C_2H_5)_2NH$)[15b] afforded methylenolactocin in less than 20% yield.
(21) A sample of natural methylenolactocin was kindly provided by Professor B. K. Park (Kang Woen National University, Korea). We observed a higher rotation (lower concentration) than that reported.
(22) That the absolute stereochemistry of the natural product is, in fact, as depicted (the formulation consistent with the expected transition-state conformation of enol ether **3**) was established by photochemical decarboxylation (Pyrex filter, acridine, *tert*-C_4H_9SH, C_6H_6, 20 °C, 3 h, 57%)[23] of acid (−)-**6** to yield (*S*)-(−)-γ-nonanolactone ($[\alpha]^{21}_D$ −48.4° (*c* 0.5, CH_3OH); lit.[24] −48.8° (*c* 1, CH_3OH)).
(23) Okada, K.; Okubo, K.; Oda, M. *Tetrahedron Lett.* **1989**, *40*, 6733–6736.
(24) Ravid, U.; Silverstein, R. M.; Smith, L. R. *Tetrahedron* **1978**, *34*, 1449–1452.
(25) Related lactones include the following: protolichesterinic acid (Asahina, Y.; Asano, M. *J. Pharm. Soc. Jpn.* **1927**, *539*, 1–17), nephromopsinic acid (Asano, M.; Azumi, T. *Chem. Ber.* **1935**, *68B*, 995–997), alloprotolichesterinic acid (Asahina, Y.; Yanagita, M. *Chem. Ber.* **1936**, *69B*, 120–125), nephrosterinic acid (Asahina, Y.; Yanagita, M.; Sakurai, Y. *Chem. Ber.* **1937**, *70B*, 227–235), avenaciolide (Brookes, D.; Tidd, B. K.; Turner, W. B. *J. Chem. Soc.* **1963**, 5385–5391), and canadensolide (McCorkindale, N. J.; Wright, J. L. C.; Brian, P. W.; Clarke, S. M.; Hutchinson, S. A. *Tetrahedron Lett.* **1968**, 727–730).

Oligonucleotides with a Nuclease-Resistant Sulfur-Based Linkage

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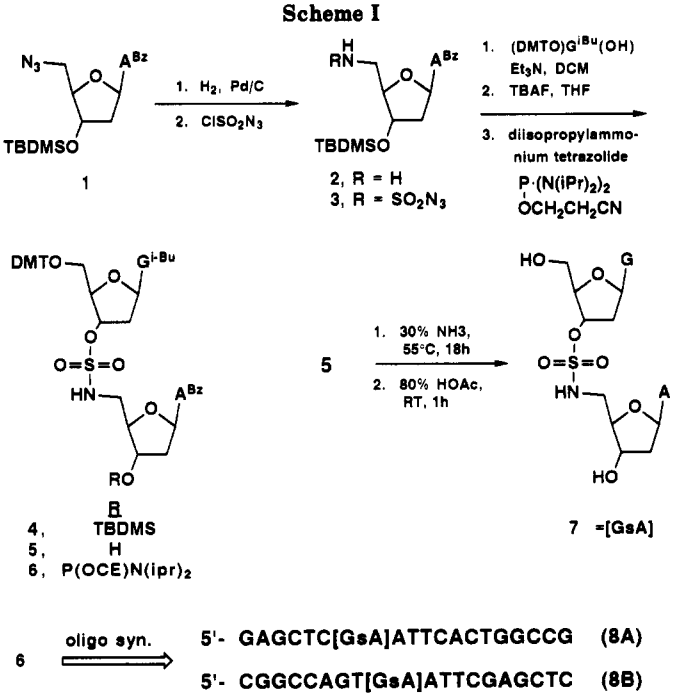
Summary: A pair of complementary oligonucleotides with an *EcoR1* recognition sequence (GÂATTC) bearing a novel sulfamate linkage at the cleavage site have been prepared and shown to be capable of annealing to form a stable duplex that is resistant to *EcoR1* cleavage.

Over the past several years there has been increasing interest in the development of nucleic acids as potential therapeutics.[1] The most common approach, known as antisense therapy, involves the use of short oligonucleotides to target regions of complementary sequence on a large nucleic acid (e.g., mRNA) for the purposes of blocking function (e.g., translation). Numerous structural modifications of oligonucleotides, most centered on the phosphodiester linkage, have been investigated in an attempt to increase lipophilicity and confer nuclease resistance.[2,3]

We have been exploring a class of oligonucleotide analogues which feature the replacement of the internucleotide phosphorus atom with sulfur.[4] For ease of synthesis and chemical stability we have also replaced the 5′-bridging oxygen with nitrogen. The resulting sulfamate linkage is neutral, achiral, and isoelectronic and isostructural with the phosphodiester. We report herein on a pair of oligo-

Scheme I



(1) Cohen, J. S., Ed. *Oligodeoxynucleotides, Antisense Inhibitors of Gene Expression*; CRC Press: Boca Raton, FL, 1989.
(2) Uhlmann, E.; Peyman, A. *Chem. Rev.* **1990**, *90*, 543–584.
(3) Zon, G. *Pharmaceut. Res.* **1988**, *5*, 539–549.
(4) For other analogues with a replacement of phosphorus with sulfur see: (a) Musicki, B.; Widlanski, T. S. *Tetrahedron Lett.* **1991**, *32*, 1267–1270. (b) Musicki, B.; Widlanski, T. S. *J. Org. Chem.* **1990**, *55*, 4231–4233. (c) Huang, Z.; Schneider, K. C.; Benner, S. A. *J. Org. Chem.* **1991**, *56*, 3869–3882. (d) Schneider, K. C.; Benner, S. A. *Tetrahedron Lett.* **1990**, *31*, 334–338. (e) Summerton, J. E.; Weller, D. D. US Patent 5,034,506, 1991.

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