

Table I. Results of the Asymmetric Aldol Reactions Using (1*R*,2*S*)-*N*-Methylephedrine

entry	R-CHO	anti/syn	anti-1/anti-2	syn-3/syn-4	% yield ^c	methyl ester 5		methyl ester 6	
						% yield	% ee	% yield	% ee
1	Ph	85:15 ^{a,b}	34:1 ^{a,b}	4.5:1 ^a	80	60	94.0 ^{d,e}	10	64.0 ^f
2	<i>n</i> -C ₅ H ₁₁	75:25 ^{a,b}	<i>g</i>	<i>g</i>	60	66	93.0 ^{d,e}	22	70.0 ^h
3	<i>n</i> -C ₃ H ₇	80:20 ^{a,b}	<i>g</i>	<i>g</i>	88	60	91.0 ^{d,e}	15	52.5 ^h
4	(<i>E</i>)-CH ₃ CH=CH	80:20 ^{a,b}	≥25:1 ^{a,b}	<i>g</i>	78	52	91.0 ^{d,h}	13	70.0 ^h
5	(<i>E</i>)-PhCH=CH	85:15 ^{a,b}	≥25:1 ^{a,b}	<i>g</i>	60	60	91.0 ^{d,h}	10	24.0 ^h

^a Ratio determined by 200-MHz ¹H NMR spectroscopy. ^b Ratio determined by isolation of the adducts (flash chromatography). ^c Overall yield of silylation and aldol condensation. ^d The methyl ester with 100% ee was easily obtained starting from the isolated major stereoisomer *anti*-1, obtained by flash chromatography. ^e The enantiomeric excess was assessed by optical rotation comparison (see ref 3a,3b) and by ¹H NMR spectroscopy in the presence of Eu(hfc)₃. ^f The enantiomeric excess was assessed by optical rotation comparison (see: Evans, D. A.; Bartroli, J.; Shih, T. L. *J. Am. Chem. Soc.* 1981, 103, 2127) and by ¹H NMR spectroscopy in the presence of Eu(hfc)₃. ^g Not detectable by ¹H NMR spectroscopy. ^h The enantiomeric excess was assessed by ¹H NMR spectroscopy in the presence of Eu(hfc)₃.

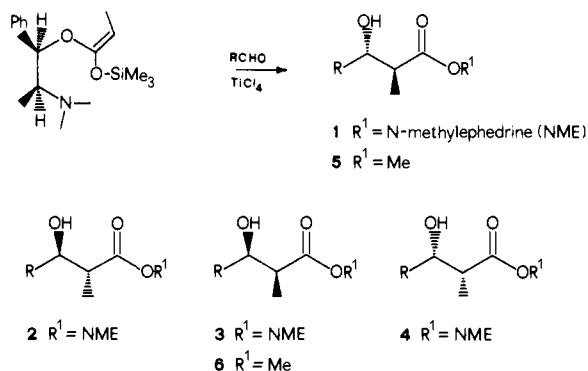


Figure 1. TiCl₄-mediated aldol reactions of the *E* silylketene acetal derived from (1*R*,2*S*)-*N*-methylephedrine-*O*-propionate leading to the major stereoisomer *anti*-1. Shown are the other isomers *anti*-2, *syn*-3, *syn*-4.

E silylketene acetal derived from (1*R*,2*S*)-*N*-methylephedrine-*O*-propionate, both the aldehyde carbonyl⁵ and the ephedrine NMe₂ group are expected to bind to TiCl₄, which usually ligates two-electron-donating molecules to form cis-octahedral, six-coordinate complexes.⁶ Therefore the conformational freedom of the system is likely to be dramatically reduced, and the C-C bond formation occurs on the six-coordinate metal in a highly stereoselective way.⁷

N-Methylephedrine (1*R*,2*S*) was treated with CH₃CH₂COC(=O)Cl in CH₂Cl₂ to give the *O*-propionate (100%). LDA enolization (THF, -78 °C) and Me₃SiCl trapping (-78 °C) gave the silylketene acetal (95%; *E/Z* ≥95:5), which was worked up by evaporation without water quenching. Addition of 1 mol equiv of the silyl ketene acetal in methylene chloride to 1 mol equiv of the TiCl₄-aldehyde complex at -78 °C in CH₂Cl₂ gave high overall yields of the aldol condensation products with remarkable stereoselectivity (Figure 1, Table I).⁸

(5) For general references to the Lewis acid-carbonyl complexation, see: Fraticello, A.; Kubo, R.; Chow, S. *J. Chem. Soc., Perkin Trans. 2* 1976, 1205. Lienard, B. H. S.; Thomson, A. J. *J. Chem. Soc., Perkin Trans. 2* 1977, 1400. Olah, G. A.; O'Brien, D. H.; Calin, M. *J. Am. Chem. Soc.* 1967, 89, 3582. Brookhart, M.; Levy, G. C.; Winstein, S. *J. Am. Chem. Soc.* 1967, 89, 1735. Grinvald, A.; Rabinovitz, M. *J. Chem. Soc., Perkin Trans. 2* 1974, 94. Thil, L.; Riehl, J. J.; Rimmelin, P.; Sommer, J. M. *J. Chem. Soc., Chem. Commun.* 1970, 591. Reetz, M. T. *Angew. Chem., Int. Ed. Engl.* 1984, 23, 556 and references therein. The crystal structure of the benzaldehyde-BF₃ complex has been recently determined (Reetz, M. T., personal communication).

(6) The crystal structure of a cis-octahedral, six-coordinate titanium complex containing a seven-membered ring chelate structure has been recently reported: Poll, T.; Metter, J. O.; Helmchen, G. *Angew. Chem., Int. Ed. Engl.* 1985, 24, 112.

(7) A detailed analysis of the possible transition states leading to the four diastereoisomers and a complete account of the observed selectivity will be given in a full paper.

(8) The stereochemical outcome of the reaction was found to be relatively independent of the silylketene acetal double-bond geometry. In fact the (*Z/E* 65:35) silylketene acetal obtained using LiN(SiMe₃)₂ as base instead of LDA gave the following result with benzaldehyde: anti/syn 80:20; *anti*-1/*anti*-2 ≥ 22:1; 65% overall yield. The stereochemical outcome is not even affected by a different mode of addition of the reagents: by treatment of the silylketene acetal first with TiCl₄ (30 min, -78 °C) and then with benzaldehyde, the same result as in Table I, entry 1 (yield and selectivity), was obtained.

The observed anti/syn ratios (3-5.6:1, Table I) are different from those reported for the related simple alkyl propionates⁴ and are markedly dependent on the π-conjugation (more conjugation, higher ratio) and on the steric hindrance (more hindrance, lower ratio) of the aldehyde used.⁹ The adducts were treated with NaOH (H₂O-MeOH, room temperature) and then with CH₂N₂ (Et₂O) to give the methyl esters in good yield and optically pure *N*-methylephedrine which could be recycled. The major stereoisomers *anti*-1 could be easily isolated by flash chromatography and converted to the optically pure methyl esters 5.

It is worth noting that both the syn and the anti methyl esters 5 and 6 have the same absolute configuration at C-2 (*S*). This shows that, while the aldehyde π-facial selectivity is only moderate, the silylketene acetal π-facial selectivity is very high.

An extension of this methodology to other reactions is under current investigation.

Supplementary Material Available: Detailed experimental procedures for the reactions, analyses, optical rotations, and spectroscopic data (¹H NMR, IR) for the compounds are provided (6 pages). Ordering information is given on any current masthead page.

(9) The anti/syn ratios worsen with aldehyde α-branching. For example: isobutyraldehyde, yield 59%; anti/syn 67:33; *anti*-1/*anti*-2 ≥ 20:1; *syn*-3/*syn*-4 ≥ 8:1.

Synthesis of Branched Ribonucleotides Related to the Mechanism of Splicing of Eukaryotic Messenger RNA

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Since Wallace and Edmonds¹ first discovered a branched structure of RNA from polyadenylated heterogenous nuclear RNAs, considerable attention has been paid to this unique structure in relation to the mechanism of RNA splicing.² Very recently, Green^{3a} and Sharp^{3b} have reported a new type of

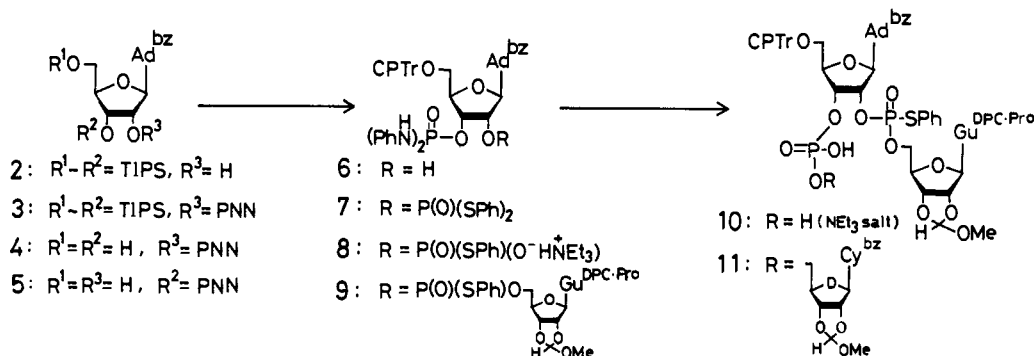
(1) Wallace, J. C.; Edmonds, M. *Proc. Natl. Acad. Sci. U.S.A.* 1983, 80, 950.

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(3) (a) Ruskin, B.; Krainer, A. R.; Matiatas, T.; Green, M. R. *Cell* 1984, 38, 317. (b) Padgett, R. A.; Konarska, M. M.; Grabowski, P. J.; Hardy, S. F.; Sharp, P. A. *Science (Washington D.C.)* 1984, 225, 898. (c) Zeitlin, S.; Efstratiadis, A. *Cell* 1984, 39, 589. (d) Rodriguez, J. R.; Pikielny, C. W.; Rosbash, M. *Cell* 1984, 39, 603. (e) Domdey, H.; Apostol, B.; Lin, R.-J.; Newman, A.; Brody, E.; Abelson, J. *Cell* 1984, 39, 611. (f) Tabak, H. F.; Van der Horst, G.; Osinga, K. A.; Arnberg, A. C. *Cell* 1984, 39, 623.

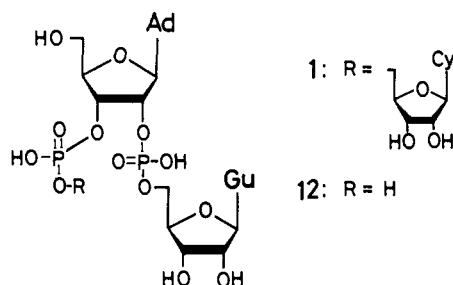
(4) Compound 2 was prepared by the procedure reported by: Markiewicz, W. T. *J. Chem. Res., Synop.* 1979, 24.

Scheme I



branched structure named as "ariat structure". Almost at the same time, similar structures have been characterized in several laboratories.^{3c-f}

In this paper we wish to report the synthesis of a branched triribonucleoside diphosphate **1**, the structure of which exists at



the branch point of the lariat structure reported by Ruskin.^{3a} For this study, *N*⁶-benzoyl-3',5'-(tetraisopropylsilyloxane-1,3-diyl)-adenosine (**2**)⁴ was chosen as starting material since we considered that this compound allowed the direct 2'-O-phosphorylation and the successive introduction of a different phosphate group into the 3'-free hydroxyl which would be generated by desilylation of the first phosphorylated product. In this project, the 2'-phosphate protecting group should be sufficiently stable upon the desilylation since in the presence of a neighboring 3'-free hydroxyl group a fully substituted 2'-phosphoryl group tends to lead to the 2',3'-cyclization.⁵ Therefore, we employed the anilino group as the phosphate protecting group since phosphorodiamidates were rather stable to basic media compared with phosphotriesters and thereby the cyclization might be avoided.⁶ However, we have encountered difficulty in introducing the dianilino phosphoroyl (PNN) group onto the 2'-oxygen of **2** by use of dianilidophosphorochloridate under the standard conditions.⁷ In order to overcome this problem⁸ we now found a new effective method for the phosphorylation of sterically hindered hydroxyl groups. When **2** was allowed to react with 1.5 equiv each of hexaethylphosphorous triamide (HEPA)⁹ and tetrazole¹⁰ in 1,2-dichloroethane at room

temperature for 10 min followed by successive treatments with 4 equiv each of aniline and tetrazole for 10 min and then with iodine in pyridine for 10 min, the desired product, **3**,¹¹ was obtained in 84% yield.

Treatment of **3** with KF-Et₄NBr in wet acetonitrile at 45 °C for 1 h¹² gave a mixture of 2'-phosphorodiamidate (**4**)¹¹ and its 3'-regioisomer **5**,¹¹ which were isolated in 37% and 57% yields, respectively. The latter was apparently formed by isomerization of the phosphate group during the fluoride ion promoted desilylation. Both the products were available for the synthesis of branched RNAs. The major product **5** was tritylated by treatment with tris(4,5-dichlorophthalimido)trityl bromide (CPTTrBr)¹³ in the presence of silver nitrate in dimethylformamide for 30 min to afford the 5'-masked adenosine derivative **6** in 57% yield. Phosphorylation of **6** with 1.5 equiv of cyclohexylammonium *S,S*-diphenyl phosphorodithioate¹⁴ in the presence of mesitylenedisulfonyl chloride¹⁵ and tetrazole¹⁶ in pyridine for 15 min gave fully protected key intermediate **7** in 81% yield.

Treatment of **7** with 3 M pyridinium phosphinate¹⁴ in pyridine (room temperature, 1 h) gave quantitatively the diester **8**. Condensation of **8** with 1.5 equiv of *N*²-propionyl-*O*-(diphenylcarbamoyl)-2',3'-*O*-(methoxymethylene)guanosine¹⁷ in the presence of isodurenedisulfonyl chloride (DDS)^{15b} and 3-nitro-1,2,4-triazole¹⁸ in pyridine (room temperature, 2 h) gave the 2'-5'-linked dimer **9** in 92% yield. Upon treatment of **9** with isoamyl nitrite¹⁹ in pyridine-acetic acid-acetic anhydride²⁰ (room temperature, 16 h), the 2'-phosphomonoester derivative **10** was obtained in 75% yield by preparative TLC (scheme I). Condensation of **11** with *N*⁴-benzoyl-2',3'-*O*-(methoxymethylene)cytidine¹⁷ in the presence of DDS in the phosphodiester method resulted in the 3'-5'-coupling product **11** in 80% yield. Full deprotection of **11** was performed by the following procedure: (1) 0.2 M NaOH-pyridine (2:1, v/v) at 0 °C for 15 min; (2) concentrated ammonia-pyridine (1:10, v/v) at 50 °C for 5 h; (3) 80% acetic acid at 25 °C for 6 h.²¹ Thus, the branched trimer **1** could be isolated in 20% yield by paper chromatography, purified by HPLC, and finally analyzed by paper electrophoresis. The *R_f*

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(7) (a) Smrt, J. *Tetrahedron Lett.* **1973**, 4727. (b) Zielinski, W. S.; Smrt, J. *Collect. Czech. Chem. Commun.* **1974**, *39*, 2483.

(8) Two research groups have reported the phosphorylation of the 2'-hydroxyl group of 3',5'-*O*-(tetraisopropylsilyloxane-1,3-diyl)adenosine: (a) Gioeli, C.; Kwiatkowski, M.; Oberg, B.; Chattopadhyaya, J. B. *Tetrahedron Lett.* **1981**, *22*, 1741. (b) Karpeisky, M. Yu.; Beigelman, L. N.; Mikhailov, S. N.; Padyukova, N. Sh.; Smrt, J. *Collect. Czech. Chem. Commun.* **1982**, *47*, 156. The latter group described the poor reactivity of the 2'-hydroxyl group even toward a powerful phosphorylating agent of 2-(chlorophenyl)-phosphorodithiazolidine.

(9) We reported previously the phosphorylation of 5'-(monomethoxytrityl)thymidine with tris(dimethylamino)phosphine for the synthesis of 5'-*O*-(monomethoxytrityl)thymidine-3'-phosphonate: Sekine, M.; Mori, H.; Hata, T. *Tetrahedron Lett.* **1979**, 1145.

(10) The activation of monofunctional nucleoside phosphoramidites with tetrazole has been reported by: Beaucage, S. L.; Caruthers, M. H. *Tetrahedron Lett.* **1981**, 1859.

(11) Compounds **3**-**10** were characterized by their ¹H NMR and ³¹P NMR spectra and elemental analyses. For example, the ³¹P NMR spectrum of the key intermediate **7** exhibited two different peaks at -1.937 and -54.737 ppm (CDCl₃, 85% H₃PO₄).

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(21) The CPTTr group can be removed by these successive treatments without use of hydrazine.¹⁶

and R_m values²² of the trimer were almost consistent with those of the corresponding linear structure, ApGpC, reported by Khorana.²³ The trimer was resistant to nuclease P₁ and ribonuclease T₂. The trimer was resistant to nuclease P₁ but digested with snake venom phosphodiesterase to give pC, pG, and A in the ratio of 1.00:0.96:1.10. These results were consistent with those reported by Ruskin²⁴ and Wallace.¹ Furthermore, structural proof of the trimer was also obtained at the level of the dimer. The main product **12**^{22,24} isolated in 79% yield by a similar deprotection procedure from **10** was incubated with alkaline phosphatase. This enzyme reaction gave quantitatively 2'-5'-linked ApG, which was found to be resistant to nuclease P₁ but yet digestible to A and pG upon treatment with snake venom phosphodiesterase. These properties were in agreement with those of 2'-5' RNAs.

Biological properties of **1** and **12** will be reported shortly in detail elsewhere.

(22) **1**: R_f 0.74 (relative to pU) (*n*-PrOH/concentrated ammonia/H₂O, 55:10:35, v/v/v); R_m 0.47 (relative to pU) (0.03 M phosphate buffer, pH 7.1), **12**: R_f 0.66; R_m 0.85.

(23) Lohrmann, R.; Söll, D.; Hayatsu, H.; Ohtsuka, E.; Khorana, H. G. *J. Am. Chem. Soc.* **1966**, *88*, 819.

(24) This type of compound is also of interest since Konarska has recently reported formation of a 2'-phosphomonoester, 3',5'-phosphodiester linkage by a RNA ligase in wheat germ: Konarska, M.; Filipowicz, W.; Domdey, H.; Gross, H. J. *Nature (London)* **1981**, *293*, 112.

Band Electronic Structures of the Ambient Pressure Organic Superconductors β -(ET)₂X (X = I₃⁻, IBr₂⁻)

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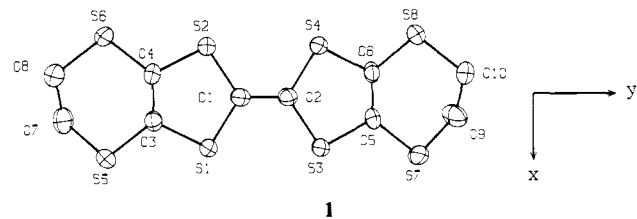
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Recently, bis(ethylenedithio)tetrathiafulvalene (BEDT-TTF or simply ET, C₁₀S₈H₈) (**1**) has been found to yield two ambient



pressure organic superconductors β -(ET)₂I₃ ($T_c = 1.2$ – 1.6 K)¹⁻⁶

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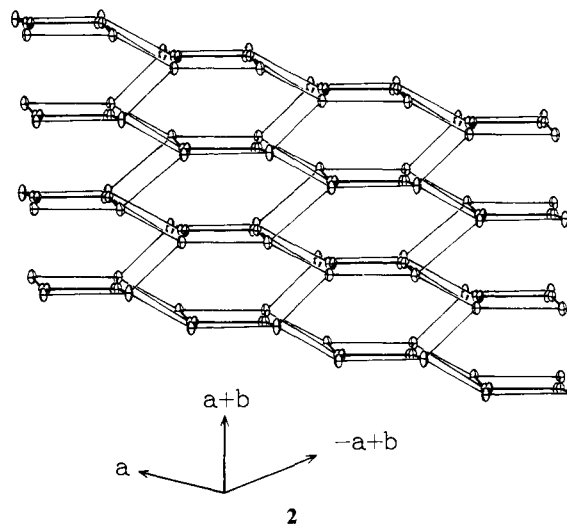
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and β -(ET)₂IBr₂ ($T_c = 2.3$ – 2.8 K).^{7,8} Crystal structures determined at two temperatures (298, 125 K) reveal^{3,7,9} that the ET stacks have a number of short interstack S...S contact distances less than the van der Waals radius sum of sulfur (3.60 Å) along the *a* and *a* + *b* directions, as shown by a schematic illustration **2** of a sheet of ET stacks projected along the local *y* axis of ET



defined in **1** (only the sulfur atoms of ET are shown in **2**, where the thin lines joining adjacent ET molecules indicate short interstack S...S contacts less than 3.6 Å). Thus the β -(ET)₂X (X = I₃⁻, IBr₂⁻) synthetic metals appear much more two dimensional (2D) in terms of crystal packing than any other known organic conductors. In the above β -(ET)₂X salts the corrugated sheets of ET stacks are separated by sheets containing anions X⁻,^{3,7} thereby leading to alternating layers of cations and anions perpendicular to *c* (*y* axis in the Cartesian system). In agreement with these structural characteristics, electrical¹⁻³ and optical¹⁰ conductivity measurements and critical magnetic field studies^{4,11} have shown that β -(ET)₂I₃ is a 2D metal. The band electronic structure¹² of β -(ET)₂I₃, estimated for the room temperature structure by calculating the overlap integrals between the HOMO's of nearest-neighbor ET molecules, indicated that the Fermi surface is closed and nearly isotropic in two dimensions. The crystal structures of β -(ET)₂X vary appreciably as a function of the anion size and temperature.^{3,7} To quantitatively evaluate how such structural changes affect the electronic structures of β -(ET)₂X, we carried our band electronic structure calculations on β -(ET)₂X (X = I₃⁻, IBr₂⁻) for the crystal structure determined at both 298 and 125 K^{3,7} employing the tight binding band scheme^{13,14} based upon the extended Hückel method.¹⁵ In order to better represent the interstack S...S interactions, double- ζ Slater-type orbitals were used for the *s* and *p* orbitals of carbon and sulfur.^{16,17}

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