R enantiomer is acylated faster than the *S* antipode in the experiments depicted in the first 10 entries of Table I (the sense of the enantioselectivity for the resolution depicted in entry 11 has not yet been established).

Crude preparations of *Pseudomonas* AK are currently available for around $1 per gram, and approximately equal masses of the substrate and enzyme preparation are used; consequently, these resolutions are extremely economical. Furthermore, the experimental procedure for these resolutions is exceedingly simple (see Table I).

Substrates resolved in this study were chosen because the corresponding asymmetric epoxidations do not work well. For instance, the allylic alcohol shown in entry 1 is unlikely to be resolved smoothly under the metal-catalyzed conditions due to decomposition of the product (as observed for epoxidation of 2-phenylallyl alcohol).[2] Similarly, 1-phenylallyl alcohol reacts slowly under metal-catalyzed conditions and with poor enantiodiscrimination[2] (cf. entry 2), and Sharpless epoxidations of 2,4-dienols, while possible,[10] generally are complicated by decomposition products[11] (cf. entry 6).

The resolutions depicted in entries 3–6 are particularly notable for two reasons. Firstly, good yields of recovered starting materials and acetate products were isolated, demonstrating that the method can be applied to such sensitive substrates. Secondly, it would be extremely difficult to obtain optically active 3-hydroxy-1-phenylpenta-1,4-diene (**3**), for instance, via the Sharpless epoxidation. The Sharpless selection rules for kinetic resolution via asymmetric epoxidation[3] imply that each enantiomer of this diene (**3**) has one reactive stereotopic face no matter what enantiomer of dialkyl tartrate is used in the catalyst; hence, epoxidations that leave unreacted starting material are possible only if one of the alkene groups reacts much faster.[12] Biocatalytic resolutions, however, provide an excellent route to optically active 1,4-dien-3-ol (**3**) and related compounds.

Entries 5 and 7–10 (Table I) indicate that acylations mediated by *Pseudomonas* AK also provide access to optically active *propargylic* alcohols. Asymmetric reductions of the corresponding ketones with Alpine-Borane (B-isopinocampheyl-9-borabicyclo-[3.3.1]nonane),[13] probably the most useful of the literature procedures[14] for preparation of such materials, are *least* enantioselective when a small group is attached to the ketone functionality. The lipase-catalyzed process is nicely complementary insofar as resolutions of alkynyl alcohols with a small substituent at the hydroxymethine center proceed with high enantiodiscrimination.

Finally, while asymmetric epoxidations of allenic alcohols are generally disappointing,[2] the biocatalytic resolution depicted in entry 11 of Table I is highly enantioselective. In fact, the main restriction on this resolution is decomposition of the product and starting material during the chromatographic separation used to purify them.

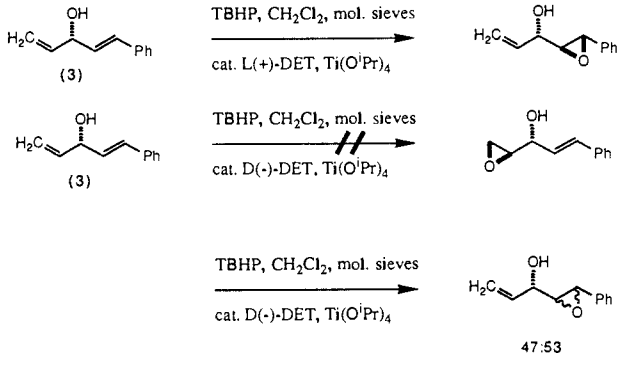
Unlike the Sharpless methodology, the resolutions described here are limited to alcohols with one relatively large and one small substituent attached to the hydroxymethine center; however, our procedure can be used to resolve substrates that are not amenable to asymmetric epoxidation. Furthermore, acylations of *R* enantiomers mediated by *Pseudomonas* AK consistently proceed faster than those of the other enantiomer, a trend that will be valuable in the planning of synthetic schemes based on this methodology. Other data, to be described in the full account of this work, indicates that *Pseudomonas* AK also mediates enantioselective acylations of some allylic alcohols that *can* be resolved via the Sharpless methodology. We believe that where both techniques are applicable, the enzyme-mediated approach is usually superior and will usurp the role of many epoxidation-based kinetic resolutions in organic synthesis.[15]

Acknowledgment. We thank the donors of the Petroleum Research Fund, administered by the American Chemical Society, and the National Institutes of Health for financial support. We also thank Amano Company, and Mr. Tominaga and Mr. Watanabe in particular, for assistance with the lipase enzymes.

(10) Falck, J. R.; Mana, S.; Siddhanta, A. K.; Capevila, J.; Bunyak, J. D. *Tetrahedron Lett.* **1983**, *24*, 5715.

(11) Bernat, B.; Vasella, A. *Tetrahedron Lett.* **1983**, *24*, 5491.

(12) Results presented below prove that the aryl-substituted alkene group is indeed more reactive than the monosubstituted alkene; epoxidation occurs on the aryl-substituted alkene for catalysts based both on L-(+)-diethyl tartrate (DET) *and* on D-(−)-DET. *Clean* epoxidation of the aryl-substituted alkene



(**3**) to one epoxide stereoisomer with the catalyst from L-(+)-DET, and epoxidation to a mixture of diastereomers with D-(−)-DET, implies the *S* configuration at the hydroxymethine center, an assertion that was confirmed via other means.

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(15) Lipase-mediated *hydrolyses* of some unsaturated compounds containing $CF_3CH(OH)$ functionality have been reported, but the enantioselectivities observed are inferior to the results reported here. See: Lin, J. T.; Yamazaki, T.; Kitazume, T. *J. Org. Chem.* **1987**, *52*, 3211.

Enantio-DNA Recognizes Complementary RNA but Not Complementary DNA

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Antisense oligonucleotides provide an attractive strategy for designing chemotherapeutic agents and biochemical tools,[1] but the biological applicability is quite limited because of the existence in cells of large amounts of nucleases. To overcome this problem, efforts to increase resistance to nucleases as well as to improve the stability of duplex (or triplex) formation have been made.[1] As oligonucleotides with a modified nucleoside unit, oligomers with an α-deoxyribose backbone instead of a natural β-deoxyribose backbone have been prepared and characterized.[2]

(1) For reviews, see: (a) Miller, P. S.; Ts'O, P. O. P. *Annu. Rep. Med. Chem.* **1988**, *23*, 295. (b) Uhlmann, E.; Peyman, A. *Chem. Rev.* **1990**, *90*, 543.

(2) (a) Morvan, F.; Rayner, B.; Imbach, J.-L.; Lee, M.; Hartley, J. A.; Chang, D.-K.; Lown, J. W. *Nucleic Acids Res.* **1987**, *15*, 7027. (b) Bloch, E.; Lavignon, M.; Bertrand, J.-R.; Pognan, F.; Morvan, F.; Malvy, C.; Rayner, B.; Imbach, J.-L.; Paoletti, C. *Gene* **1988**, *72*, 349. (c) Imbach, J.-L.; Rayner, B.; Morvan, F. *Nucleosides Nucleotides* **1989**, *8*, 627.

0002-7863/90/1512-7436$02.50/0

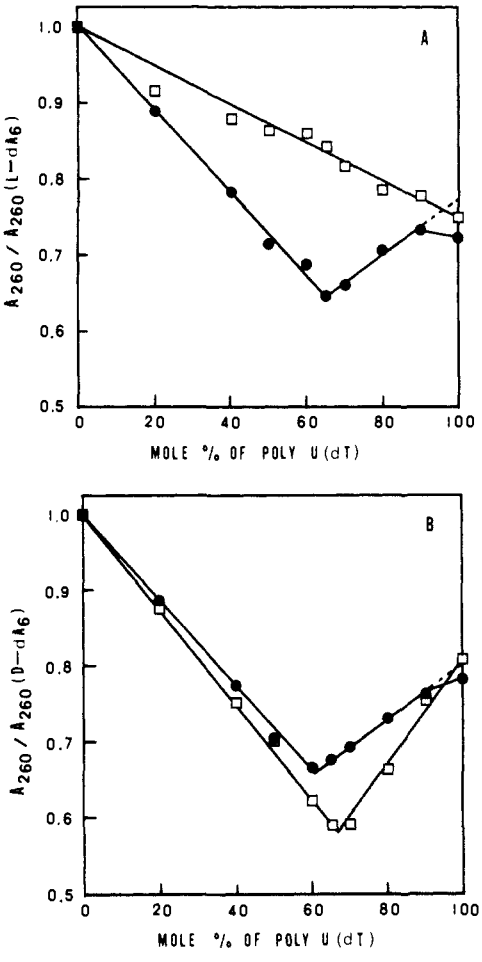


Figure 1. UV mixing curves for interactions of L-dA$_6$ (A) and D-dA$_6$ (B) with homopolynucleotides [poly(U) (●), poly(dT) (□)] in 10 mM Tris (pH 7.4)/10 mM $MgCl_2$ at 0 °C.

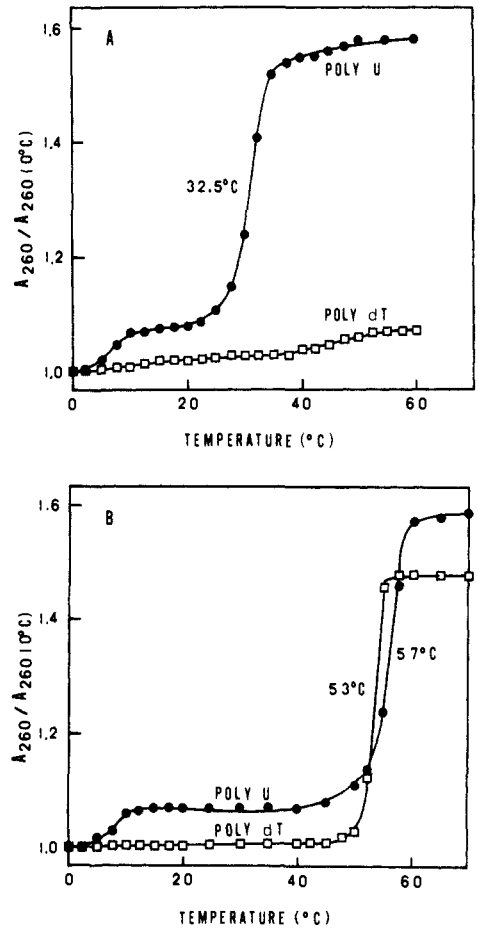


Figure 2. T_m measurement for L-dA$_6$/poly(U or dT) complex (A) and D-dA$_6$/poly(U or dT) complex (B) in 10 mM Tris (pH 7.4)/10 mM $MgCl_2$.

Another possible sugar modification involves the use of enantio-DNA (DNA with 2-deoxy-L-*erythro*-pentose instead of 2-deoxy-D-ribose as a sugar backbone). We considered that enantio-DNA would not be a substrate for nucleases and that it would hybridize with the complementary oligo(deoxy)nucleotides. Though a few papers have appeared on enantiooligonucleotides,[3-5] little has been established about the nature of the interactions of enantiooligonucleotides with RNA or DNA. Such considerations prompted us to synthesize a hexamer of enantiodeoxyadenylic acid [L-(dAp)$_5$dA, designated as L-dA$_6$] and to investigate the interaction of L-dA$_6$ with the complementary polymers such as poly(U) (RNA type) and poly(dT) (DNA type).

The enantiomer of 2'-deoxyadenosine (L-dA) was synthesized by a direct glycosylation as described by Robins et al.,[6] from 2-deoxy-L-*erythro*-pentose (prepared from L-arabinose by the glycal method[7]). L-dA was protected (*N*,*N*-dibenzoyl-5'-dimethoxytrityl) and phosphorylated with quinolyl dihydrogen phosphate to give protected deoxy-L-adenylic acid (L-dAp). The protected L-dAp was coupled in a stepwise manner by the usual triester method[8] to give hexamer (L-dA$_6$) after deprotection. L-dA$_6$ thus synthesized was purified by HPLC (ODS/0.1 M Et_3NHOAc–9% CH_3CN) and obtained as Et_3NH salt after lyophilization. The structure and the purity were confirmed by 400-MHz ^1H NMR and HPLC (the purity was at least 95%).

L-dA$_6$ was resistant to bovine spleen phosphodiesterase, as expected; no decomposition of L-dA$_6$ was detected during incubation of the compound with bovine spleen phosphodiesterase (25 units/mL) in NH_4OAc buffer (pH 6.5) at 37 °C for 1 h, though the corresponding natural hexamer (D-dA$_6$) was completely hydrolyzed under the same conditions.

To investigate the interaction of L-dA$_6$ with polynucleotides, we measured UV mixing curves in 10 mM Tris pH 7.4/10 mM $MgCl_2$ by the method of continuous variations[9] at first (Figure 1). The UV mixing curve for interaction of L-dA$_6$ with poly(U) shows maximum hypochromicity (ca. 22%) at an approximate 1:2 molar ratio (35% L-dA$_6$) of L-dA$_6$ to poly(U), which indicates triple-helix formation.[10] The profile of the UV mixing curve, as well as the value of maximum hypochromicity, was very close to that for the interaction of natural hexamer (D-dA$_6$) with poly(U),[10] suggesting similarity of the conformations between the enantio-DNA/natural RNA complex and the natural DNA/natural RNA complex. L-dA$_6$ did not show any hypochromicity when mixed with poly(G), poly(A), or poly(C), as was also the case with D-dA$_6$.[11] It is particularly noteworthy that L-dA$_6$ also did not show any hypochromicity when mixed with complementary poly(dT), though natural D-dA$_6$ did show apparent hypochromicity[12] when mixed with poly(dT). On this basis we may

(3) Synthesis of L-ApA and its very weak interaction (T_m = 5–5.6 °C) with poly(U). Tazawa, I.; Tazawa, S.; Stempel, L. M.; Ts'o, P. O. P. *Biochemistry* **1970**, *9*, 3499.

(4) Synthesis of L-(dUp)$_{17}$dU and the absence of interaction of the compound with poly(dA). Anderson, D. J.; Reischer, R. J.; Taylor, A. J.; Wechter, W. J. *Nucleosides Nucleotides* **1984**, *3*, 499.

(5) Synthesis of L-(dAdT)$_3$. No description of the interaction of the compound with other oligo- or polynucleotides. Rákóczy, P.; Ötvös, L. *F.E.C.S. Int. Conf. Chem. Biotechnol. Biol. Act. Nat. Prod., Proc., 3rd* **1985** (**1987**), *4*, 101.

(6) (a) Robins, M. J.; Khwaja, T. A.; Robins, R. K. *J. Org. Chem.* **1970**, *35*, 636. (b) Kazimierczuk, Z.; Cottam, H. B.; Revankar, G. R.; Robins, R. K. *J. Am. Chem. Soc.* **1984**, *106*, 6379.

(7) Deriaz, R. E.; Overend, W. G.; Stacey, M.; Teece, E. G.; Wiggins, L. F. *J. Chem. Soc.* **1949**, 1879.

(8) Takaku, H.; Morita, K.; Sumiuchi, T. *Chem. Lett.* **1983**, 1661.

(9) Job, P. *Anal. Chim. Acta* **1928**, *9*, 113.

(10) (dA)$_{10}$·2(dT)$_{10}$ triple helix. Pilch, D. S.; Levenson, C.; Shafer, R. H. *Proc. Natl. Acad. Sci. U.S.A.* **1990**, *87*, 1942.

(11) Mixing of L-dA$_6$ or D-dA$_6$ with poly(G) showed hyperchromicity which could not be explained by base-pairing.

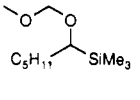
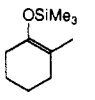
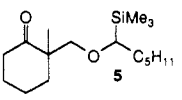
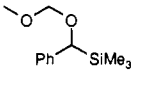
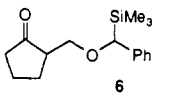
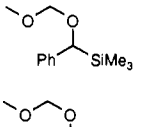
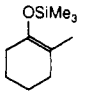
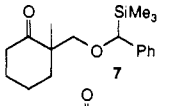
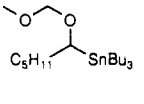
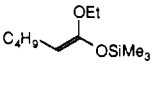
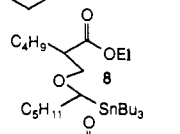
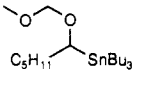
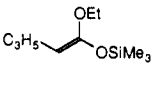
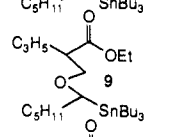
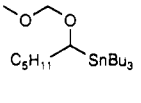
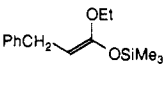
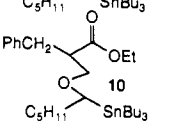
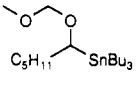
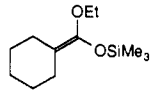
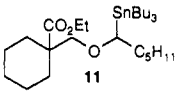
hypothesize that enantio-DNA in general recognizes complementary RNA specifically but not complementary DNA. It would be a characteristic feature of enantio-DNA, because natural DNA (and natural RNA) normally recognizes both complementary DNA and RNA.

Next we investigated the melting temperature (T_m) for interaction of L-dA_6 with polynucleotides (Figure 2).[10] The T_m profiles also demonstrated that L-dA_6 interacts with poly(U) but not with poly(dT). The T_m value of the L-dA_6/poly(U) complex was determined to be 32.5 °C under the experimental conditions used. The T_m values of D-dA_6/poly(U) and D-dA_6/poly(dT) complexes were determined to be 57 and 53 °C, respectively (in good coincidence with the reproted values). The higher T_m value of the D-dA_6/poly(U(dT)) complex than of the L-dA_6/poly(U) complex reflects the higher stability of the former than of the latter. Though the L-dA_6/poly(U) complex is less stable than the D-dA_6/poly(U) complex, L-dA_6 possesses the striking ability to distinguish RNA from DNA. Anderson et al. reported that L-$(dUp)_{17}$dU did not interact with poly(dA).[4] We predict that L-$(dUp)_{17}$dU should interact with poly(A) (RNA type).

Our results suggest that enantio-DNAs may have a characteristic ability to be RNA-specific antisense oligonucleotides. Such RNA-specific oligonucleotide analogues have not previously been reported to our knowledge. As a tool for biochemical research, enantio-DNAs would give a low background in various kinds of biological assays because of the RNA specificity, stability to nucleases, and nonnatural character. Investigations to study applications of enantio-DNAs having specific base sequences as biochemical tools and as chemotherapeutic agents are planned.

(12) The values of the hypochromicity were in good accordance with the reported values. Cassani, G. R.; Bollum, F. J. *Biochemistry* **1969**, *8*, 3928.

Table I. Directed Aldol Reactions of Mixed Acetals

Entry	Acetal	Nucleophile	Aldol Product	Yield,%[a] (Method)[b]
1			 **5**	99 (A)
2			 **6**	40 (A)
3			 **7**	48[c](A) 79 (B)
4			 **8**	93 (C)
5			 **9**	83 (C)
6			 **10**	73 (C)
7			 **11**	73 (C)

[a] Isolated yields of analytically pure material. [b] Reaction conditions: A, 1.1 equiv of $TiCl_4$, CH_2Cl_2, −78 °C; B, 0.05 equiv of Me_3SiOTf, 0.05 equiv of 2,6-di-*tert*-butylpyridine, CH_2Cl_2, reflux; C, 0.9 equiv of $TiCl_4$, CH_2Cl_2, −78 °C. [c] Side products related to the formation of a benzyl cation intermediate reduced the yield. Method B provides an alternative procedure to A which results in improved yields of the aldol product; see entry 3.

Furanone Synthesis via an Electrophilic Capped Carbonyl Ylide

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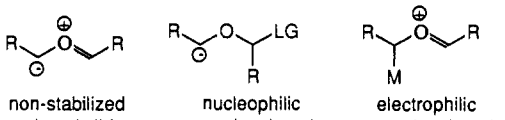
The synthesis of tetrahydrofurans (THFs) commonly proceeds via C–O bond formation, while the application of C–C bond forming reactions for this purpose is not common.[1] 1,3-Dipolar cycloaddition reactions[2] have provided nitrogen heterocycles via azomethine ylides; however, the extension of this approach to THF synthesis by carbonyl ylides has not been as successful. Carbonyl ylides may be generated by carbene additions to carbonyls,[3] by photolysis or thermolysis of oxiranes,[4] or by thermal decomposition of oxadiazolines.[5] Recently, Padwa and co-workers[6] have made considerable progress in the generation and reaction of stabilized carbonyl ylides; however, successful methods for nonstabilized ylides are still lacking. We have recently reported a new method for the regiospecific synthesis of THFs via a nucleophilic carbonyl ylide synthon,[7] and we report here our extension of this concept to the generation and reaction of an electrophilic carbonyl ylide synthon.



non-stabilized carbonyl ylide | nucleophilic capped carbonyl ylide (LG = leaving group) | electrophilic capped carbonyl ylide (M = masked anion)

We reasoned that the Mukaiyama reaction[8] could be applied to the electrophilic carbonyl ylide synthon problem provided that

(1) For a recent review on the synthesis of THFs, see: Boivin, T. L. B. *Tetrahedron* **1987** *43*, 3309–3362. For recent examples of C–C bond forming reactions leading to THFs, see, inter alia: Broka, C. A.; Shen, T. *J. Am. Chem. Soc.* **1989**, *111*, 2981–2984. Feldman, K. S.; Fisher, T. E. *Tetrahedron* **1989**, *45*, 2969–2977. Middleton, D. S.; Simpkins, N. S.; Terrett, N. K. *Tetrahedron Lett.* **1988**, *29*, 1315–1318 and references therein.

(2) For a general discussion of synthetic, mechanistic, and theoretical aspects of dipolar cycloaddition reactions, see: *1,3-Dipolar Cycloaddition Chemistry*; Padwa, A., Ed.; Wiley-Interscience: New York 1984.

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(6) For some recent examples from this research group, see the following references and earlier references cited therein: Dean, D. C.; Krumpe, K. E.; Padwa, A. *J. Chem. Soc., Chem. Commun.* **1989**, 921–922. Padwa, A.; Chinn, R. L.; Zhi, L. *Tetrahedron Lett.* **1989**, *30*, 1491–1494. Padwa, A.; Hertzog, D. L.; Chinn, R. L. *Tetrahedron Lett.* **1989**, *30*, 4077–4080. Padwa, A.; Hornbuckle, S. F.; Frypell, G. E.; Stull, P. D. *J. Org. Chem.* **1989**, *54*, 817–824.

(7) Linderman, R. J.; Godfrey, A. *J. Am. Chem. Soc.* **1988**, *110*, 6249–6251.

(8) Mukaiyama, T. *Org. React. (N.Y.)* **1982**, 203–326.

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