

TA)₂; d(TATATGCGCATATA)₂ (**2**); d(ATACGCGTAT)₂; d(ATATACGCGTATAT)₂. The spectral changes induced by ActD, after accounting for the flanking sequences, are extremely similar for all oligomers with the GCGC sequence. In Figure 1 imino proton spectra of **1** at various ratios of ActD are shown and are compared to a spectrum for **2** at the 2:1 ratio. Spectral changes at ratios of 1.0 and below are quite complex and indicate the presence of two 1:1 complexes. At the 2.0 ratio the spectra simplify and indicate the presence of a unique 2:1 complex for both **1** and **2**. In contrast, titrations of duplexes containing the sequence CGCG give very similar spectra with evidence for formation of only a single 1:1 species at the GC site.

³¹P NMR titrations of **1** with ActD are shown in Figure 2 and a spectrum for **2** at a ratio of 2.0 is included for comparison. Four of five phosphodiester groups of **1** were labeled with ¹⁷O and the assignments (Figure 2) employ the numbering scheme T-1-G-2-C-3-G-4-C-5-A. As ActD is added to **1**, a complex pattern of downfield peaks appears which are identified in the 0.5 ratio spectrum. As can be seen, there are two sets of downfield signals for P2 and P4 which represent two different 1:1 complexes at GC base pairs.

All 1:1 complexes with ActD studied here and described previously^{8,10,18,19} have downfield ³¹P signals between -1 and -3 ppm and between -2 and -3 ppm. With the CGCG oligomers, as with most other oligomers investigated by NMR to this time, the GC binding site is on the duplex C2 symmetry axis and orientation of the unsymmetric ActD in either possible direction, with the peptides in the minor groove, produces an identical complex. With **1** and **2**, however, binding of a single ActD at either GC site gives two different complexes, which are a consequence of the two possible orientations of ActD in an intercalation site,⁸ and this accounts for the two sets of downfield peaks obtained in the ³¹P spectra in Figure 2 at ratios up to 1.0. The peak areas for the two adducts suggest similar, but not identical, energetics in their DNA binding with the driving force largely a result of the peptide-DNA interactions. At the 2.0 ratio only single signals for P2 and P4 are shifted significantly downfield (-2 to -3 ppm region). In principle three different 2:1 complexes, two with C2 symmetry, are possible but the spectral simplification (relative to the 1:1 complexes) indicates that a unique complex with C2 symmetry is formed. It seems likely that steric constraints on the actinomycin cyclic peptides force the 2:1 complex into a single bound configuration. The shift differences among the 1:1 and 2:1 complexes in ³¹P spectra are, no doubt, a consequence of differences in ring current effects, torsional angles, hydrogen bonding, and other similar factors which are not yet fully understood.^{8,10,18,19}

Several new points are quite clear from these results. First, with these oligomers there is no significant length dependence in the observed effects of ActD binding. Comparison of Figures 1 and 2 illustrates that the six bp's of **1** exhibit imino and ³¹P shifts on addition of ActD which are similar to the shifts for the central six bp's of **2**. Indeed d(GCGC)₂, which has no flanking sequences, also gives similar results. Second, ActD binds to GC sequences with a much higher preference than to CG or any other sequence in these oligonucleotides. All oligomers which have two CG and a single GC site, for example, form only a 1:1 complex with ActD and the binding site is the GC site as evidenced by imino proton shifts induced by the anisotropic ring current of the phenoxazone ring. Both **1** and **2**, on the other hand, have two GC sites and one CG site and form 1:1 and 2:1 complexes. The ³¹P shifts for the five phosphodiester groups of **1** indicate that the 1:1 complexes are at either of the GC sites while the 2:1 complex has ActD bound at both GC sites. Third, the spectra in Figures 1 and 2 contain

the first direct evidence for formation of two 1:1 complexes by the unsymmetric phenoxazone ring of ActD as suggested by Krugh and co-workers based on chemical shift analysis of ActD-dinucleotide complexes.⁸ This is the first direct evidence for multiple 1:1 complexes for unsymmetrical intercalators and raises important questions about multiple binding orientations of intercalators, in general. Fourth, this finding indicates that the exclusion limit of ActD is quite small (it can intercalate at adjacent GC sites). DNase I footprinting studies have suggested that binding of ActD at a GC site can inhibit binding at other GC sites up to four bp's away.²⁰ The NMR and footprinting results may not be in disagreement, however, since the more stable 1:1 complexes are almost completely formed before any significant amount of the 2:1 complex is seen (Figures 1 and 2). We are currently investigating oligomers with longer runs of adjacent GC sites to define the exclusion limit and structural effects of ActD binding in more detail.

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Enantioselective Conjugate Addition of Rationally Designed Chiral Cuprate Reagents to 2-Cycloalkenones

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Evidence has been obtained recently that the conjugate addition reaction of Gilman reagents with α,β -enones can follow a pathway involving (1) reversible d, π^* -complexation of nucleophilic copper with the enone, (2) β -cuprio adduct formation, and (3) reductive elimination to give the β -carbon adduct.^{1,2} With this mechanistic guidance it became of interest to evaluate appropriate chiral reagents which might deliver copper enantioselectively to one face of an α,β -enone, both as a test of the mechanistic hypothesis and a step toward more powerful synthetic methodology. Described herein are results of an initial investigation that demonstrate for the first time the possibility of achieving useful enantioselectivities (75-95%) with a simple chiral controller ligand (**1**), obtainable in one step in either enantiomeric form from inexpensive (+)- or (-)-ephedrine.

Reaction of (1*R*,2*S*)-(-)-ephedrine (**2**) with 1.16 equiv of (2-chloroethyl)dimethylamine hydrochloride and 2 equiv of powdered potassium carbonate in ethanol at reflux for 4 h afforded after vacuum concentration, extractive isolation, filtration through silica gel (20:1 ethyl acetate-triethylamine), and Kugelrohr distillation [160 °C (0.1 torr)] 82% yield of amino alcohol **1**, [α]_D²³ +1.86° (*c* 1.2, chloroform). This ligand was then deprotonated (1 equiv of RLi), complexed with cuprous iodide (dissolved in tetrahydrofuran (THF)-dimethyl sulfide), and treated with additional RLi to generate the complexed cuprate reagent.

Experiments on the conjugate addition of *n*-butyl to 2-cyclohexenone revealed a strong dependence of the results on the purity of the organolithium reagent. Thus, with a fresh bottle of the purest *n*-butyllithium available (as a clear solution in hexane) to make the chiral reagent, an 80% yield of 1,4-adduct of 88% ee was obtained. Otherwise, identical experiments with older bottles

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O-silylation of the chiral ligand in the mixed cuprate at $-78\text{ }^{\circ}\text{C}$.

The chiral ligand **3**, $[\alpha]_{\text{D}}^{23} +105.1^{\circ}$ (c 2.5, chloroform), and its enantiomer are available starting with (*R*)-(-)- or (*S*)-(+)-mandelic acid, respectively.¹⁶ Conversion of **3** to the chiral mixed methyl cuprate using methyl lithium reagent in ether and toluene as the other solvent afforded a homogeneous reagent which upon reaction at $-78\text{ }^{\circ}\text{C}$ with 2-cyclohexenone afforded in 60% yield (*R*)-(+)-3-methylcyclohexanone of 90% ee. Although less work has been done with **3** because its synthesis requires four steps, it is obviously an effective ligand for enantioselective conjugate addition.

The results reported herein represent a major advance from earlier findings with chirally complexed cuprates⁹ and provide a strong indication that excellent progress is possible in this area. The study of other ligands should yield valuable information.¹⁷

(16) The synthetic sequence used for the synthesis of **3** was as follows: (1) conversion of mandelic acid to the acetate (acetyl chloride, 98% yield); (2) formation of acid chloride (thionyl chloride, 99% yield); (3) reaction with trimethylethylenediamine (96% yield); (4) reduction with lithium aluminum hydride (90% yield) to form **3**, $[\alpha]_{\text{D}}^{23} -106.0^{\circ}$ (c 1.5, CHCl_3).

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Importance of the Timing of Bond Breaking and Bond Making in Acetal Templates. Enantiodivergent Synthesis of Steroidal Side Chains[†]

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Asymmetric syntheses via chiral acetal templates are becoming increasingly important for modern organic chemistry.¹ A mechanistic rationale which readily accounts for the observed high asymmetric induction is provided by Johnson and Bartlett.^{1b,c} However, an important unanswered question remains concerning the timing of bond breaking and bond making in the chiral cyclic acetal templates. The $\text{S}_{\text{N}}2$ -like transition state is proposed, and thus a fully synchronous process must be needed for the high asymmetric induction. In other words, the enantiomeric excess or even the direction of asymmetric induction should strongly depend upon both the Lewis acidity of MX_n and the nucleophilicity of Nu.²

However, to the best of our knowledge, the results reported until now do not show such a sign.³ We herein report for the first time

[†] Dedicated to Professor G. Zweifel on the occasion of his 60th birthday.

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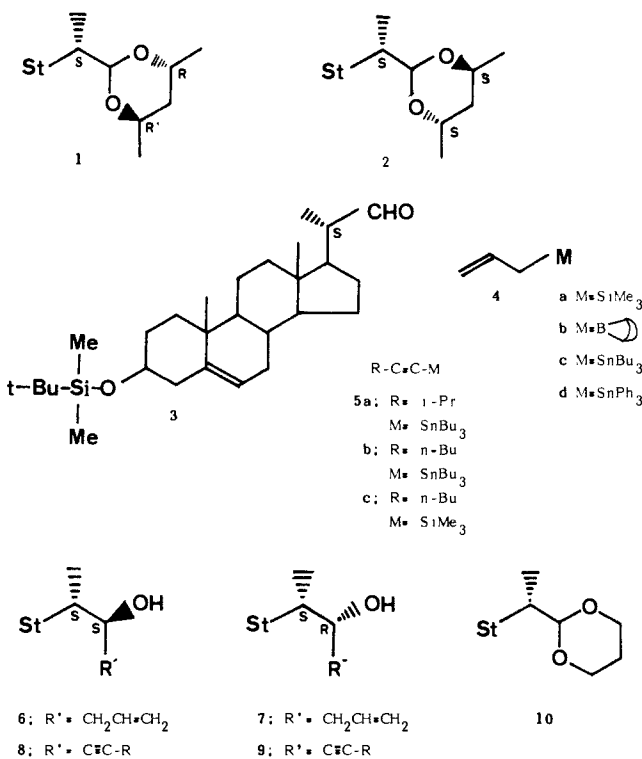
Table I. Enantiodivergent Synthesis of Steroidal Side Chains^a

entry	steroidal acetal	organo-metal	isomer ratio ^b	isolated yield, %	chirality of a major isomer ^c	
					template	Cram rule
1	1 (<i>S</i> - <i>R,R</i>)	4a	>99:<1	93	+	+
2		4b	>99:<1	90	+	+
3		4c	96:4	85	+	+
4	2 (<i>S</i> - <i>S,S</i>)	4a	90:10	93	-	+
5		4b	88:12	88	-	+
6		4c	30:70	84	+	-
7		4d	76:24	80	-	+
8	1 (<i>S</i> - <i>R,R</i>)	5a	6:7	80	+	+
9		5b	95:5	82	+	+
10		5c	98:2	72	+	+
11	2 (<i>S</i> - <i>S,S</i>)	5a	10:90	78	+	-
12		5b	8:92	78	+	-
13		5c	92:8	82	-	+

^a All reactions were carried out on 1-mmol scale according to the literature procedure.^{1b-d} The isomer ratio of the final products were essentially identical with those of the initial adducts (steroidal ethers). ^b By 400-MHz ¹H NMR spectroscopy (supplementary material). ^c (+) The chirality of a major isomer is consistent with the chirality predicted either by the template or by Cram rule. (-) The chirality of a major isomer is opposite from the predicted chirality.

evidence that the bond making and bond breaking are in fact concerted for the high asymmetric induction via acetal templates and an enantiodivergent synthesis of a steroidal side chain by use of this concept.

Treatment of the chiral steroidal acetal **1** (*S*-*R,R* isomer), prepared from the steroidal aldehyde **3**⁴ and (*2R,4R*)-(-)-pentanediole,⁵ with allylsilane **4a** in the presence of TiCl_4 followed by the usual workup^{1b} gave **6** exclusively. On the other hand, the



(3) Organomagnesium, -lithium, -copper, -silicon, and -aluminum compounds exhibit the same tendency in chiral induction; the *R,R* acetal induces *S* chirality and the *S,S* acetal induces *R* chirality; ref 1 and references cited therein.

(4) The chiral aldehyde was prepared from pregnenolone by the literature procedure: Midland, M. M.; Kwon, Y. C. *Tetrahedron Lett.* **1984**, 5981.

(5) Purchased from Waco Chemical Ind., Japan.