# Chiral Acetal Induced Asymmetric Polyene Tetracyclization Assisted by a Cation-Stabilizing Auxiliary[1]

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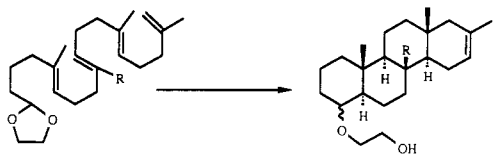
*Summary:* Previous methodology for chiral acetal initiated asymmetric cyclizations has now been applied to a tetracyclization assisted by a cation-stabilizing (C-S) auxiliary. Thus the *S,S* acetal **12**, having the isobutenyl C-S auxiliary at pro-C-8, undergoes cyclization to give, as the major product, the compound **16** having the complete steroid nucleus with "natural" configuration. Removal of the chiral auxiliary gives **18**, which was shown to be 90% ee.

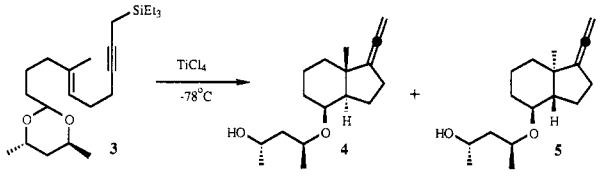
*Sir:* Beneficial effects on polyene cyclizations have been realized by the expedient of introducing cation-stabilizing (C-S) auxiliaries at positions on the substrate where carbocationic character is presumed to develop in the transition state of the process. For example, the yield of tetracyclic products (having all-trans ring fusions) obtained from cyclization of the tetraenic acetal **1b** with the isobutenyl C-S auxiliary at pro-C-8, was 77%[1a] as compared with 30% for the cyclization of **1a**.[2]




1a R = H 2a

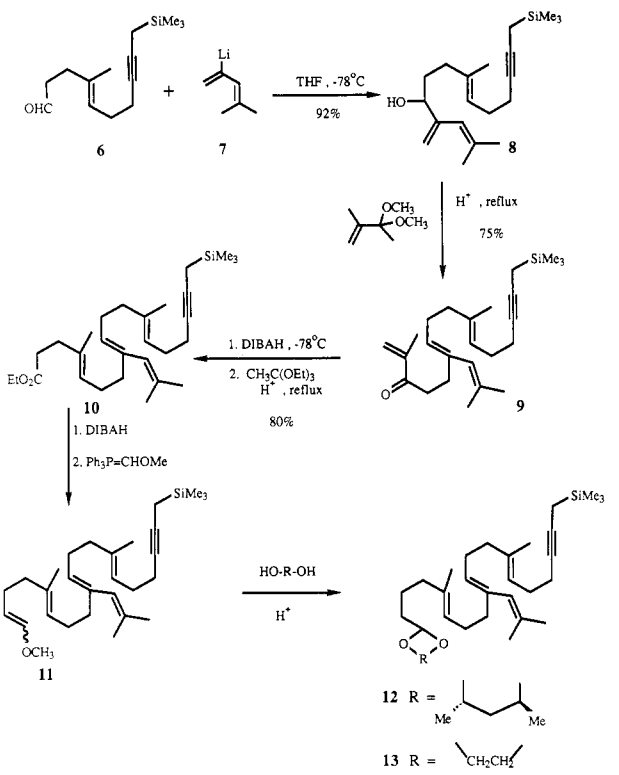
1b R = -C=CMe$_2$ 2b

The objective of the present study was to use chiral acetal methodology[3] to initiate an asymmetric tetracyclization assisted by a C-S auxiliary. Hitherto such asymmetric cyclizations have been used only to form bicyclic products.[4] Considering the case of the cyclization of *S,S* acetal **3** to give **4** and **5** in 87:13 selectivity and 92% ee,[4a] we elected to aim our study toward the preparation and cyclization of the substrate **12** having the same initiator and terminator functions as in the model **3**. The tetracyclization of **12** was envisioned as being assisted by the C-S (isobutenyl) auxiliary at pro-C-8, yielding the complete steroid nucleus in the natural enantiomeric form.




The synthesis of substrate **12** was accomplished by the same basic strategy that was developed for making **1b**.[1a] Thus the trienyne carbinol **8**, obtained on reaction of the lithio diene **7** with the known aldehyde **6**,[5] was submitted to an olefinic ketal Claisen rearrangement,[6] giving the unsaturated ketone **9** (Scheme I). Reduction of **9** to the corresponding allylic alcohol, followed by an orthoacetate Claisen rearrangement, afforded the ester **10** in 60% overall yield from aldehyde **6**. Conversion of **10** into the corresponding aldehyde, followed by Wittig coupling with

**Scheme I**




methoxymethyltriphenylphosphorane, gave the enol ethers **11**, which on treatment with 2(*S*),4(*S*)-pentane-2,4-diol[7] and a trace of *p*-toluenesulfonic acid in refluxing benzene gave acetal **12** in 63% yield (from **10**) after normal-phase HPLC to remove traces of geometric isomers formed in the Claisen reactions. The ethylene glycol acetal **13** was similarly prepared (69% overall yield from ester **10**) for use in exploratory cyclizations.

The most favorable cyclization conditions found were employed in the following preparative experiment. Treatment of **13** (0.15 mmol) with 5.5 equiv of 6:5 $TiCl_4/Ti(OiPr)_4$[8] in pentane containing 1 equiv of 2,6-

† NATO Science Postdoctoral Fellow (1986–1987).

‡ The X-ray analyses reported herein were performed by U.S. at the Institut für Anorganische Chemie der Universität Würzburg.

(1) This paper represents paper 3 on cation-stabilizing auxiliaries in polyene cyclizations. For the first two papers in the series, see: (a) Johnson, W. S.; Telfer, S. J.; Cheng, S.; Schubert, U. *J. Am. Chem. Soc.* **1987**, *109*, 2517–2518. (b) Johnson, W. S.; Lindell, S. D.; Steele, J. *J. Am. Chem. Soc.* **1987**, *109*, 5852–5853.

(2) Johnson, W. S.; Wiedhaup, K.; Brady, S. F.; Olson, G. L. *J. Am. Chem. Soc.* **1968**, *90*, 5277–5279. Johnson, W. S.; Wiedhaup, K.; Brady, S. F.; Olson, G. L. *J. Am. Chem. Soc.* **1974**, *96*, 3979–3984.

(3) For paper 15 of this series, see: Johnson, W. S.; Kelson, A. B.; Elliott, J. D. *Tetrahedron Lett.* **1988**, *29*, 3757–3760.

(4) (a) Johnson, W. S.; Elliott, J. D.; Hanson, G. *J. Am. Chem. Soc.* **1984**, *106*, 1138–1139. (b) For the seminal work on asymmetric bicyclizations, see: Johnson, W. S.; Harbert, C. A.; Stipanovic, R. D. *J. Am. Chem. Soc.* **1968**, *90*, 5279–5280. Johnson, W. S.; Harbert, C. A.; Ratcliffe, B. E.; Stipanovic, R. D. *J. Am. Chem. Soc.* **1976**, *98*, 6188–6193.

(5) Schmid, R.; Huesmann, P. L.; Johnson, W. S. *J. Am. Chem. Soc.* **1980**, *102*, 5122–5123.

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(7) Aldrich material, shown to be 97.6% ee, containing 0.84% of meso.

(8) Prepared as described in Johnson, W. S.; Crackett, P. H.; Elliott, J. D.; Jagodzinski, J. J.; Lindell, S. D.; (in part) Natarajan, S. *Tetrahedron Lett.* **1984**, *25*, 3951–3954.

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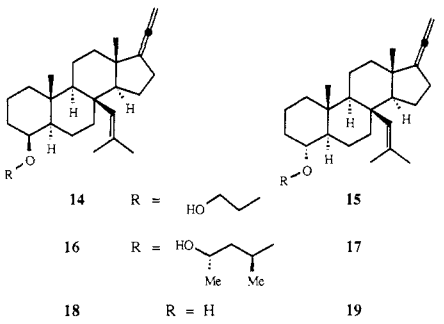
di-*tert*-butylpyridine for 1 h at −5 °C, followed by quenching with methanol, then ether, and dilute HCl, gave after flash chromatography two major components representing a 45% yield of the C-4 axial isomer **14** and 22% of the equatorial epimer **15**. The structures and relative configurations of these *racemic* materials were established unequivocally by X-ray analysis of the purified crystals, mp 142–144 °C (compound **14**) and 145–146 °C (compound **15**). Several byproducts, e.g., the TMS ethers of **14** and **15**, were isolated from the reaction mixture, raising the total yield of all-trans ring-fused products to 76%.




The 6:5 mixed catalyst used above for the cyclization of acetal **13** was too mild for the less reactive chiral acetal **12**, which, after several exploratory experiments using racemic material, was cyclized as follows. To a solution of acetal **12** (39 mg, 0.076 mmol), 2,6-di-*tert*-butylpyridine (0.038 mmol), and tetracosane (1.3 mg as a GC internal standard) in pentane (6.6 mL) at −45 °C was added a freshly prepared (see above) solution of $TiCl_4$ (0.23 mmol) and $Ti(OiPr)_4$ (0.076 mmol) over a 15-min period via a motorized syringe. After an additional 20 min at −45 °C, methanol (300 μL) and triethylamine (50 μL) were added, and the mixture was worked up with ether and dilute HCl. The ratio of axial to equatorial product was estimated to be 9:1 by GC. Filtration through a short column of silica gel gave 34.5 mg of crude axial isomer **16** (purity 70% by GC). The chiral auxiliary was removed from this crude product via the established procedure[4a] involving oxidation to the ketone followed by β-elimination. Thus, after purification by flash chromatography, a 61% yield (overall from acetal **12**) of axial **18** and 2.4% of equatorial product **19** were obtained. Further purification by reverse-phase HPLC (10% ether in $CH_3CN$) gave pure **18** (42% yield), $[\alpha]^{23}_D$ −13.6° ($c$ = 0.0062 g/mL, $CCl_4$). The optical purity of this material was determined, as in the model series,[4a] by GC analysis (base-line separation) of the Mosher esters to be 90% ee. The relative configuration of this product follows from the unequivocally established constitution of product **14** (X-ray analysis, see above). That the absolute configuration is that of the natural steroids (formula **18**) is assured by the established stereochemical course of the cyclization of **3**[4] as well as of many related reactions of chiral acetals.[3] It also follows from prior art[9] that the minor equatorial isomer has the antipodal steroid configuration *enantio*-**19**.

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**Supplementary Material Available:** Characterization data, including IR and NMR spectra as well as C, H analyses, for new compounds as well as ORTEP plots for substances **14** and **15** (8 pages). Ordering information is given on any current masthead page.

(9) See ref 4 and citations therein.

# Preparation of Alkylchromium Reagents by Reduction of Alkyl Halides with Chromium(II) Chloride under Cobalt Catalysis

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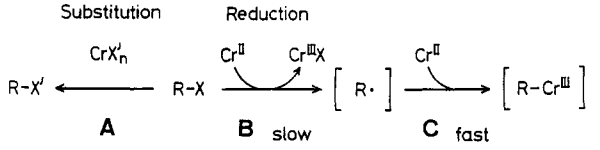
*Summary:* Alkyl halides and tosylates are reduced with $CrCl_2$ in the presence of a catalytic amount of vitamin $B_{12}$ or cobalt phthalocyanine to give alkylchromium reagents, which add to aldehydes without affecting the coexisting ketone or ester groups.

*Sir:* Notwithstanding the widespread utility of traditional organometallic reagents such as RLi and RMgX, certain limitations in their use have yet to be satisfactorily addressed. As a consequence of their high basicity and nucleophilicity, these compounds tolerate only a small number of functional groups, making it difficult to discriminate effectively between the different acceptor sites on a polyfunctional substrate molecule. Organotitanium,[1] -chromium,[2] -zinc,[3] -copper,[4] and -lead[5] reagents have provided a solution to the difficulty. Organotitanium, -copper, and -lead reagents are usually prepared through transmetalation from RLi or RMgX. Compared to the transmetalation methods, however, direct preparation through the reduction of organic halides with low-valent metals has some advantages. For instance, reagents with functional groups subject to nucleophilic attack such as ketones, esters, and nitriles could be prepared without the need for prior protection of these groups. Thus we undertook the preparation of various alkylchromium reagents, through

**Scheme I**

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