presumably, account for most of the observed olefinic and rearranged products. According to this hypothesis the substitution products derive largely from conformer **1**, whereas the elimination and rearrangement products are derived primarily from conformers **3a** and **3b**, perhaps via a common hydrogen-bridged intermediate, **4**.

As the relative abundance of the major conformational forms largely determines the extent to which these different reactions take place and neither hydrogen nor hydroxide ion are directly involved, there is no significant change in product composition with a change of 10^8 in hydrogen ion concentration.

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Stereoselective Aldol Coupling of Cobalt-Complexed Alkynyl Aldehydes

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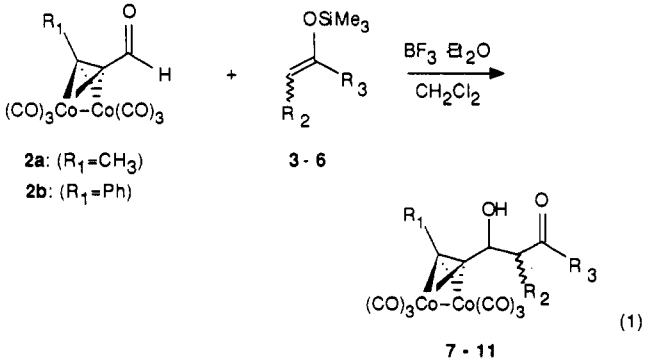
Summary: Although alkynyl aldehydes undergo crossed aldol condensation with trimethylsilyl enol ethers with little stereoselectivity, their dicobalt hexacarbonyl derivatives react with moderate to excellent syn diastereoselectivity. The selectivity is significantly dependent on the structure of the enol derivative and on temperature but relatively insensitive to the Lewis acid and the complex structure. The stereochemical assignment has been confirmed in one case by an X-ray crystal structure determination.

Sir: Despite intense interest in stereoselective C-C bond construction via aldol-type condensation reactions,[1] surprisingly little is known of the prospects for aldol coupling of alkynyl aldehydes.[2,3] The resulting acetylenic aldols are not only of interest in their own right, e.g. their presence in the remarkable macrocyclic antitumor antibiotics esperamycin and related compounds,[4] but also because the synthetic versatility of the C-C triple bond promises to make such compounds useful synthetic intermediates. Studies, primarily in this laboratory, have demonstrated the broad synthetic utility of [(propargylium)$Co_2(CO)_6$]BF_4 complexes (**1**) as propargyl cation synthons,[5] and, recently, results from Schreiber's group[6,7] and our own[8-10] have begun to realize the potential of these complexes in stereocontrolled C-C bond formation. In this report we present our initial findings on the contrasting Lewis acid promoted reactions of alkynyl aldehydes and their cobalt-complexed counterparts **2** with silylenol ethers. The latter reactions have been found to proceed with moderate to excellent syn stereoselectivity. Subsequent demetalation of these products provides a convenient stereocontrolled route to β-hydroxy-γ-acetylenic ketones.

The requisite alkynyl aldehyde complexes **2** are conveniently prepared in nearly quantitative yield from the reaction of dicobalt octacarbonyl with the alkynyl aldehyde (hexane, 20 °C, 3 h) or by facile acidic hydrolysis of the corresponding acetal complexes (THF/dilute HCl, 20 °C, 1 h).[11] Treatment of an equimolar mixture of **2a** or **2b** and silylenol ethers **3-5** in CH_2Cl_2 with 1-3 equiv of BF_3·Et_2O results in rapid production (15 min) of the corresponding aldol product complexes **7-10**, isolated in good yield following addition of Et_3N and aqueous workup (eq 1, Table I). The major product in each case at -78



2a: (R_1=CH_3) **2b**: (R_1=Ph) **3-6** **7-11** (1)

°C was assigned a syn stereochemistry on the basis of its ^1H NMR characteristics[12] and, for verification, by X-ray diffraction of the predominant isomer of **8** (ref 13, Figure 1). Efficient coupling of complex **2b** with silyl ketene acetal **6** (E/Z = 6:1) proceeded under identical conditions to afford ester derivative **11**; however, the major product in this case is assigned an anti stereochemistry.[14]

Several additional important features of the reactions of the complexed acetylenic aldehydes should be noted from the table: (1) both *E*- and *Z*-enol derivatives give syn product preferentially; (2) the degree of selectivity, how-

(1) Reviews: (a) Heathcock, C. H. In *Asymmetric Synthesis*; Academic Press: New York, 1984; Vol. 3, p 111. (b) Evans, D. A.; Nelson, J. V.; Taber, T. R. *Top. Stereochem.* **1982**, *13*, 1.

(2) (a) Coupling with a boron enolate: Evans, D. A.; Cherpeck, R. E.; Tanis, S., unpublished results cited in ref 1a. (b) Coupling with enol silanes (no stereochemistry indicated): Angoh, A. G.; Clive, L. J. *J. Chem. Soc., Chem. Commun.* **1984**, 534.

(3) Very recently some stereoselective aldol reactions of alkynyl ketones with enol silanes have been reported: Kobayashi, S.; Matsui, S.; Mukaiyama, T. *Chem. Lett.* **1988**, 1491.

(4) Magnus, P.; Lewis, R. T.; Huffman, J. C. *J. Am. Chem. Soc.* **1988**, *110*, 6921. Schreiber, S. L.; Kiessling, L. L. *Ibid.* **1988**, *110*, 631. Danishefsky, S. J.; Mantlo, N. B.; Yamashita, D. S. *Ibid.* **1988**, *110*, 6890. Nicolaou, K. C.; Zuccarello, G.; Ogawa, Y.; Schweiger, E. J.; Kuzawa, T. *Ibid.* **1988**, *110*, 1690. Kende, A. S.; Smith, C. A. *Tetrahedron Lett.* **1988**, *29*, 4217. Tomioka, K.; Fujita, H.; Koga, K. *Ibid.* **1989**, *30*, 851.

(5) Nicholas, K. M. *Acc. Chem. Res.* **1987**, *20*, 207.

(6) Schreiber, S. L.; Sammakia, T.; Crowe, W. E. *J. Am. Chem. Soc.* **1986**, *108*, 3128.

(7) Schreiber, S. L.; Klimas, M. T.; Sammakia, T. *J. Am. Chem. Soc.* **1987**, *109*, 5749.

(8) Padmanabhan, S.; Nicholas, K. M. *Tetrahedron Lett.* **1982**, 2555.

(9) Montana, A. M.; Nicholas, K. M.; Khan, M. A. *J. Org. Chem.* **1988**, *53*, 5193.

(10) Tester, R.; Varghese, V.; Montana, A. M.; Khan, M.; Nicholas, K. M. *J. Org. Chem.*, in press.

(11) Representative procedures and spectroscopic data for all new compounds are provided in the supplementary material.

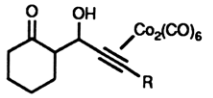
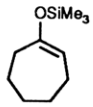
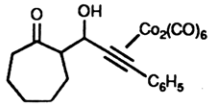
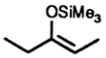
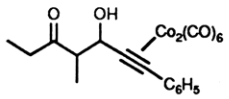
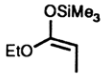
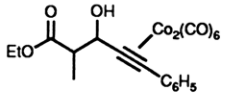
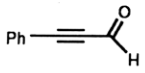
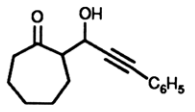
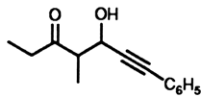
(12) The C*H*OH resonances for the syn isomers uniformly appear at lower field than those of the anti isomers ($\Delta\delta$ ca. 0.5 ppm); the former were also characterized by a smaller vicinal coupling constant (2-5 Hz vs 6-7 Hz for the anti); see ref 1a (pp 115-118) for supporting discussion.

(13) X-ray crystal data for *syn*-**8** is available in the supplementary materials.

(14) The C*H*OH resonance for the major isomer of **11** was at higher field than for the minor isomer (5.45 vs 5.64 ppm) and exhibited a larger vicinal coupling (6.7 vs 4.2 Hz) as well, consistent with an anti arrangement.

0022-3263/89/1954-5426$01.50/0

Table I. Enol Silane Alkylation by Acetylenic Aldehydes and Their $Co_2(CO)_6$ Complexes 2[a]

entry	enol silane	aldehyde	T, °C	product	% yield[b]	syn/anti
1		**2a**	−78		82	1.7:1
2	**3**		20	**7** (R = CH_3)	81	1:3
3	**3**	**2b**	−78	**8** (R = C_6H_5)	80	4.3:1
4	**3**		20		83	1.5:1
5	 **4**	**2b**	−78	 **9**	84	32:1
6	 **5**	**2b**	−78		79	32:1
7			20	**10**	80	6:1
8	 **6** (6:1 E, Z)	**2b**	−78	 **11**	82	1:4
9	**4**	 **12**	−78	 **13**	86	1:1.7
10	**5**	**12**	−78	 **14**	70	1:1.1

[a] All reactions run in CH_2Cl_2 for 15 min with 1.0 equiv of BF_3·Et_2O. [b] Yield following workup.

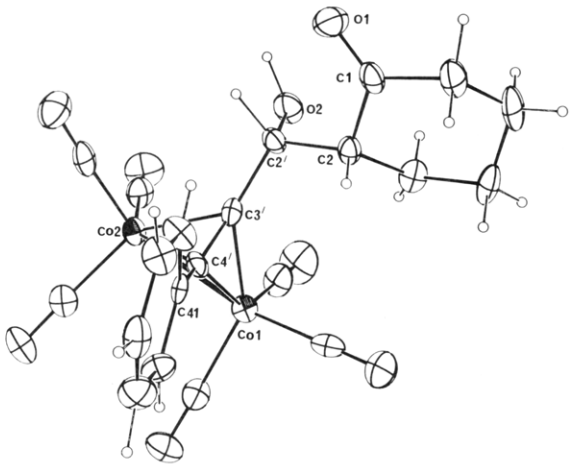


Figure 1. X-ray molecular structure of *syn*-**8**.

ever, is strongly dependent on the structure of the enol derivative (note especially entries 3, 5, 7); (3) the selectivity is relatively insensitive to the alkyne substituent (e.g. entries 1, 3), in contrast to the reactions of the parent alkyl-substituted propargylium complexes with silyl enol ethers;[6] and (4) the reactions exhibit significant temperature-dependent selectivity (entries 1, 2; 3, 4; 6, 7) with the syn preference being enhanced at lower temperature. This effect is apparently kinetic in origin since the isolated isomers of **8** were found to be stable under the reaction conditions at 20 °C and little change in the product ratio was observed when a completed reaction at −78 °C was allowed to warm to room temperature before hydrolysis.

The powerful stereodirecting effect of the cobalt carbonyl unit is underscored by comparison of the above results with the corresponding reactions of the free acetylenic aldehyde **12** with silyl enol ethers **4**, **5** in which case the acetylenic aldols **13**, **14** were formed with little or no stereoselectivity (entries 9, 10). The organocobalt unit thus serves to "bulk up" the typically stereochemically "skinny" alkyne group.[15] Finally, several other Lewis acid catalysts, including $TiCl_4$, Ph_3CBF_4, $SnCl_4$, and $Me_3SiOSO_2CF_3$ were tested in the reaction of **2b** with **3**; these were generally inferior in terms of efficiency but gave similar syn stereoselectivity (2–3:1) as BF_3·Et_2O.

Our structure/selectivity data are too limited at this time to assign a transition-state structure with confidence. Either least hindered *synclinal*[16,17] or *antiperiplanar* arrangements can accomodate the observed syn selectivity, but the latter appears more likely with the cyclic enol derivatives since it avoids severe crowding between the bulky organocobalt unit, the ring, and the $OSiMe_3$ groups. The apparent reversal of selectivity for the silyl ketene derivative parallels the stereoselectivity observed with simple aldehydes[18] and illustrates the subtle balance of factors influencing the stereochemical outcome.[19] It is

(15) For illustrations see: (a) ax/eq preference in cyclohexanes: Jensen, W.; Bushweller, C. H. *Adv. Alicycl. Chem.* **1971**, *3*, 139. (b) Ring opening of cyclopropylethynyl carbinols: Descoins, C.; Samain, D. *Tetrahedron Lett.* **1976**, 3529. (c) Claisen rearrangement: Bancel, S.; Cresson, P. *C. R. Acad. Sci. Paris* **1970**, *270*, 2161.

(16) Seebach, D.; Golinski, J. *Helv. Chem. Acta* **1981**, *64*, 1413.

(17) A synclinal transition state has been proposed[6] for reactions of the parent (propargylium)$Co_2(CO)_6^+$ complexes with acyclic silyl enol ethers.

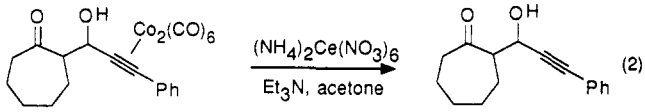
(18) Chan, T. H.; Aida, T.; Lau, P. W. K.; Gorys, V.; Harpp, D. N. *Tetrahedron Lett.* **1979**, *42*, 4029.

(19) Solution NMR studies[7,20] of the parent (RC≡CCR_2)$Co_2(CO)_6^+$ complexes reveal a dynamic structural behavior which allows rapid rotation of the CR_2 group relative to the alkyne–cobalt core.

(20) Padmanabhan, S.; Nicholas, K. M. *J. Organomet. Chem.* **1977**, *125*, C45.

interesting to note that the related coupling reactions of acetylenic acetal complexes $[RC{\equiv}CCH(OR)_2]Co_2(CO)_6$ show a significantly different pattern of selectivity with these same enol derivatives[10] probably reflecting the differing steric and electronic requirements of the OR vs O-Lewis acid groups in the transition state.

Efficient demetalation of the complexes is effected upon their treatment with ceric ammonium nitrate (acetone, Et_3N, 0 °C) as illustrated by the isolation (>95% yield) of aldol 13 from complex 9 (eq 2). The convenient introduction and removal of the directing $Co_2(CO)_6$ unit



(2)

combined with the selectivity of the cobalt-mediated aldol coupling thus provides a unique method for the stereoselective synthesis of acetylenic aldols. Efforts are underway to expand the scope and explore the applications of these reactions in natural products synthesis.

Acknowledgment. We thank Dr. Angel Montana for helpful discussions and Dr. H. Daniel Hodes for some initial experiments. We are grateful for support provided by the National Institutes of Health (Grant GM 34799) and to Pressure Chemical Co. for a gift of cobalt carbonyl.

Supplementary Material Available: Representative synthetic procedures; spectroscopic properties of new compounds; tables of X-ray coordinates, thermal parameters, bond lengths, bond angles, and associated data for *syn*-8; and copies of the ^1H NMR spectra of complexes 7-11 (18 pages). Ordering information is given on any current masthead page.

An Optically Active Terpenic Synthon for Δ^9-Cannabinoids: Synthesis of (−)-11-Hydroxy-Δ^9-tetrahydrocannabinol (THC) and Its 1′,1′-Dimethylheptyl Analogue

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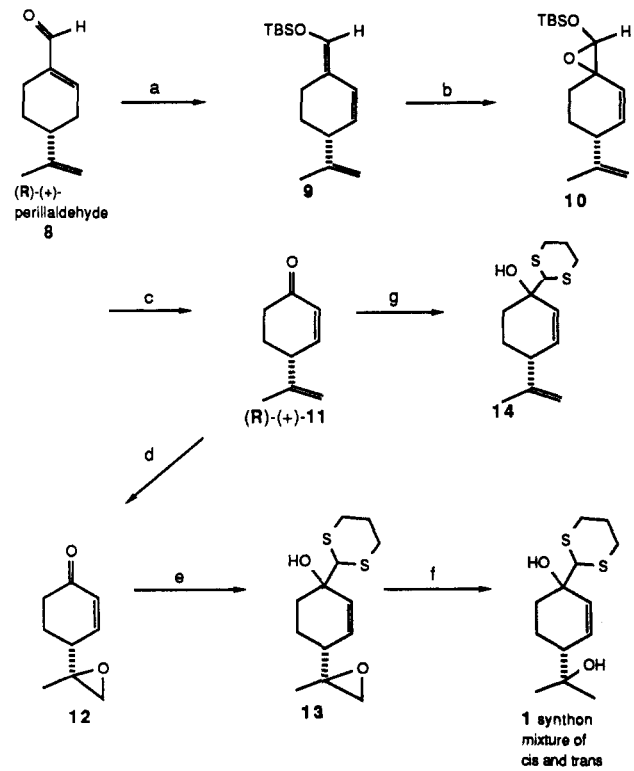
Summary: A facile entry into Δ^9-tetrahydrocannabinoids has been achieved via synthon 1, synthesized from (*R*)-(+)-perillaldehyde in a six-step process (23% overall yield).

Sir: Several years ago we reported[1] an entry into Δ^9-tetrahydrocannabinoids via a terpenic synthon carrying a 1,3-dithiane moiety. The remarkable finding in this approach was that, under acid catalysis formation, the presence of the 1,3-dithiane group effectively inhibited the isomerization of the Δ^9-unsaturation to the thermodynamically more stable Δ^8-position in the THC ring system.[2] In view of the fact that the instability of the Δ^9-unsaturation occurs in metabolites and other derivatives of Δ^9-THCs, this 1,3-dithiane containing synthon had, we felt, great potential for the synthesis of a variety of hitherto inaccessible metabolites.[2] We were unable to exploit the potential of those findings since the optically inactive terpenic synthon would lead to only racemic products.

In recent attempts to overcome this problem, we have been examining various approaches including the use of a readily available, enantiomerically pure terpene precursor to the optically active synthon 1. The recent report, by Tius and Kerr[3] for the synthesis of (*R*)-(+)-perillaldehyde (8) from commercially available (+)-limonene oxide and its conversion to 11-hydroxy-Δ^9-THC (**6a**),[4] a major metabolite of Δ^9-THC, now prompts us to record our findings in this area.

We have found that (*R*)-(+)-perillaldehyde (8, Scheme I, $[\alpha]^{26}_D$ = +128.6° (158 mg/mL, CH_3OH) [lit.[3] $[\alpha]^{19}_D$ = +128.8° ($CHCl_3$)] is an excellent starting terpene for the synthesis of the optically active synthon 1. In our approach, 8 was converted to the epoxy silyl ether **10** via the silyl enol ether **9** using essentially the same reaction conditions reported by Tius and co-workers;[4] however,

Scheme I[a]



[a] (a) TBSOTf, Et_3N, CH_2Cl_2, 0 °C; (b) MCPBA, diethyl ether–aqueous $NaHCO_3$, 25 °C; (c) HF, $NaIO_4$, CH_3CN–H_2O, 25 °C (55% overall for *a*–*c*); (d) MCPBA, CH_2Cl_2, 87%; (e) *n*-BuLi, 1,3-dithiane, THF, 60%; (f) $LiAlH_4$, diethyl ether, 78%; (g) *n*-BuLi, 1,3-dithiane, THF, 90%.

(1) Uliss, D. B.; Handrick, G. R.; Dalzell, H. C.; Razdan, R. K. *J. Am. Chem. Soc.* **1978**, *100*, 2929.

(2) For the dibenzopyran numbering system used in this paper and review of cannabinoid synthesis, see: (a) Razdan, R. K. In *Total Synthesis of Natural Products*; Ap Simon, J., Ed.; John Wiley: New York, 1981; Vol. 4, pp 186–262. (b) Mechoulom, R.; McCallum, N. K.; Burstein, S. *Chem. Rev.* **1976**, *76*, 75.

(3) Tius, M. A.; Kerr, M. A. *Synth. Commun.* **1988**, *18*, 1905.

(4) Tius, M. A.; Gu, X.; Kerr, M. A. *J. Chem. Soc., Chem. Commun.* **1989**, 62.

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