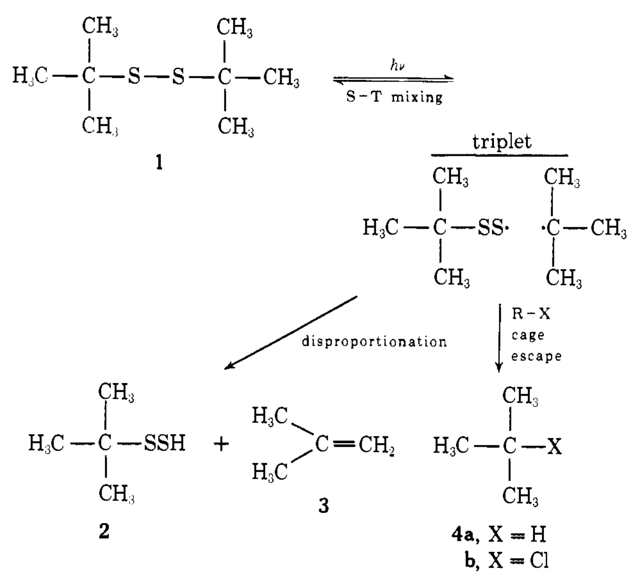
Scheme II



trations. Also, the intensity of the vinyl protons of **3** exhibits an unusual time dependence (first quite intense, rapidly diminishing to half the original value), which may well result from the formation of an efficient *tert*-butyl radical scavenger, *e.g.*, *tert*-butyl mercaptan, as a reaction product. (No information on the fate of the perthiyl fragment[11] is obtained in the nmr experiments both because the unpaired electron in the perthiyl radical is too weakly coupled to the CH_3 protons and because the S–H proton signal in **2** is probably broadened.)

The photolysis of **1** in carbon tetrachloride (sensitized or direct) shows **3** again in emission, a much weaker absorption signal from **4a**, and an enhanced absorption for *tert*-butyl chloride (**4b**). The absence of CIDNP in the starting disulfide itself is relevant to the reported[5] quantum yield of 0.34 for the formation of **4b** in the benzophenone-sensitized photolysis of **1** in carbon tetrachloride. One of the possibilities suggested to explain the low quantum yield was that recombination of the geminate radical pair might serve as an effective route for radiationless return of the excited triplet state to the ground-state singlet. Comparison of the integrated intensities of the methyl protons of starting material and isobutylene during benzophenone-sensitized photolysis of **1** in benzene yields a minimum ratio of disproportionation to recombination of 34:1, provided that the spin–lattice relaxation times of the protons in the two compounds are the same.[12] This indicates that recombination of *tert*-butyl and perthiyl radicals is at most a minor pathway for deactivation of the triplet state of **1**, although recombination of two *tert*-butyl mercapto radicals would have been undetected and could still be important. Direct and acetophenone- or benzophenone-sensitized photolysis of benzyl disulfide in benzene produces enhanced absorption in the starting material (methylenes), however, consistent with cage recombination proceeding from C–S cleavage of a triplet excited state.

Weak emission signals from **3** and enhanced absorption from **4a** and **4b** are also observed during the direct- and benzophenone-sensitized photolysis of *tert*-butyl sulfide in carbon tetrachloride, supporting other reports of C–S bond cleavage as a primary photochemical process in photolysis of simple sulfides.[13]

Since it is known that cystine residues are generally the site of enzyme photoinactivation[14] and that in solutions of pH >5 C–S cleavage in cystine is far more important than S–S cleavage,[15] several attempts were made to observe CIDNP signals during the direct and sensitized photolysis of aqueous solutions of cystine. The absence of polarization may well be due to a low quantum yield for this process.

It is somewhat surprising that for the sulfide and the two disulfides discussed here, the unsensitized photolysis produces a radical pair from a triplet state. Apparently, the rate of intersystem crossing is competitive with dissociation occurring from the photoexcited singlet. Further, it has previously been suggested that both **3** and **4a** may be produced in the photolysis of **1** from *tert*-butyl radicals which escape the geminate cage.[5a] Our results, however, support geminate disproportionation as at least a contributing process in the formation of **3**.

Acknowledgments. This work was supported by grants from the National Science Foundation and the Petroleum Research Fund, administered by the American Chemical Society. We are grateful to Dr. J. A. Kampmeier for helpful comments and a preprint.

(11) D. Grant and J. Van Wazer, *J. Amer. Chem. Soc.*, **86**, 3012 (1964).

(12) It is likely that T_1 for these two sets of protons will be quite similar: T. L. Penred, A. M. Pritchard, and R. E. Richards, *J. Chem. Soc. A*, 1009 (1966).

(13) W. E. Haines, G. L. Cook, and J. S. Ball, *J. Amer. Chem. Soc.*, **78**, 5213 (1956).

(14) K. C. Smith and P. C. Hanawalt in "Molecular Photobiology," K. C. Smith and P. C. Hanawalt, Ed., Academic Press, New York, N. Y., 1969, p 85.

(15) W. Forbes and W. Savige, *Photochem. Photobiol.*, **1**, 1 (1962).

(16) Alfred P. Sloan Foundation Research Fellow.

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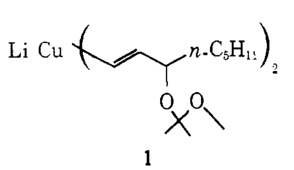
Received July 27, 1972

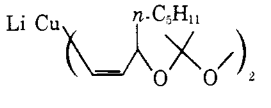
Synthesis of 13-*cis*-Prostaglandins *via* a Highly Stereoselective Conjugate Addition with a Functionalized Organocopper Reagent[1]

Sir:

We recently reported a synthesis of (−)-PGE_1 which had as its key step a conjugate addition with the *trans*-divinyl cuprate **1**[2] to the unsaturated ketone **7b**. We now report results from the conjugate addition of the *cis*-divinyl cuprate **2** which, in contrast to the *trans*-divinyl cuprate **1**, affords 1,4 adducts in high yields and, more importantly, with a very high degree of stereoselectivity.



1



2

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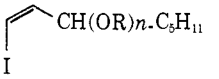
(1) Publication No. 424 from the Institute of Organic Chemistry. Studies in Prostaglandins. XI. For the previous paper in this series see ref 2.

(2) A. F. Kluge, K. G. Untch, and J. H. Fried, *J. Amer. Chem. Soc.*, **94**, 7827 (1972). See also: C. J. Sih, P. Price, R. Sood, R. G. Salomon, G. Peruzotti, and M. Casey, *ibid.*, **94**, 3643 (1972).

The *cis*-iodovinylcarbinol **3a** was prepared in *ca.* 65% yield from the acetylenic carbinol **4a**. The THP derivative **4b** in diethyl ether at −50° was treated sequentially with *n*-butyllithium and iodine. The resulting iodoacetylene **4c** was reduced readily with diimide (methanol–dipotassium azodicarboxylate–acetic acid) to give the *cis*-vinyl iodide **3b**.[3] Hydrolysis of **3b** (65% dichloroacetic acid, 2 hr at 20°) afforded **3a**.[4,5] The stereochemistry of **3a** is assigned to be cis based on the method of synthesis and on the nmr spectrum of **3c** (prepared through diimide reduction of the iodoacetylene derived from **4d**) which showed a cis coupling (7.5 Hz) of the olefinic protons.[6]

Treatment of **3c** with *n*-butyllithium in hexane at *ca.* −70° produced the *cis*-vinyllithium, which was demonstrated by quenching with D_2O to give **6** [71% isolated yield, J_{12} = 10.2 Hz; the deuterio trans isomer, J_{12} = 17 Hz). Treatment of **3d** (from **3a**, isopropenyl methyl ether, and phosphorus oxychloride) with *n*-butyllithium in hexane (*ca.* −70°) gave the *cis*-vinyllithium, and this solution when mixed with 0.5 equiv of bis(trimethyl phosphite)copper(I)iodide in diethyl ether at *ca.* −50°[2] gave the *cis*-divinyl cuprate reagent **2**.[7]



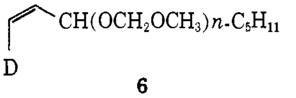
3a, R = H
b, R = THP
c, R = CH_2OCH_3
d, R = $C(CH_3)_2OCH_3$

$XC{\equiv}CCH(OR)n\text{-}C_5H_{11}$

4a, R = X = H
b, R = THP; X = H
c, R = THP; X = I
d, R = CH_2OCH_3; X = H

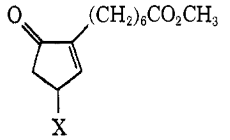
$ICH_2CH_2CH(OH)n\text{-}C_5H_{11}$

5

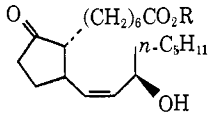


6

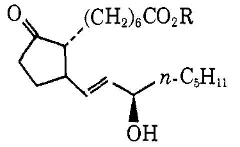
Reaction of 1 equiv of **2** with 1 equiv of the cyclopentenone **7a**[8] (*ca.* −70° for 2 hr) gave *dl*-**8a** (60%, 0.6 equiv) after mild acid hydrolysis (20% acetic acid, 20 min, room temperature).[9] Hydrolysis of the ester *dl*-**8a** with potassium hydroxide in methanol gave the acid *dl*-**8b**: mp 75.5–76.5°;[5] ir (KBr) 3350 (br, OH), 1740, 1725 (CO) cm^{-1}; nmr ($CDCl_3$) δ 5.45 (m, 2, olefinic protons); mass spectrum (70 eV) *m/e* 338 (M^+). The assignment of 15β stereochemistry is based on the isomerization of *dl*-**8a** to *dl*-**9a**.[10]



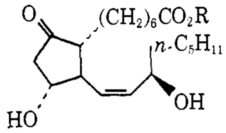
7a, X = H
b, X = $OC(CH_3)_2OCH_3$
c, X = OH



8a, R = CH_3
b, R = H



9a, R = CH_3
b, R = H



10a, R = CH_3
b, R = H

Reaction of 3 equiv of **2** with 1 equiv of **7b**[2] (*ca.* −70° for 2 hr) gave *dl*-**10a** (70%, 0.7 equiv)[9] after mild acid hydrolysis,[2] which after enzymatic hydrolysis[2] gave *dl*-**10b**: mp 87–87.5°;[5] ir (KBr) 3400 (br OH), 1740, 1725 (CO) cm^{-1}; nmr ($CDCl_3$) δ 5.5 (m, 2, olefinic protons); mass spectrum (70 eV) *m/e* 336 (M − H_2O). The stereochemistry at C-15 was assigned from ORD (*vide infra*) and by analogy to the result from the 11-desoxy PGE$_1$ case (*dl*-**8b**).

The isolation of **8a** and **10a** as single pairs of enantiomers can only have been the result of a highly stereoselective addition of the *R* enantiomer of *dl*-cuprate **2** to C-3 of the β face of the enones[11] **7a** and (*R*)-**7b** and of the *S* enantiomer of the *dl*-cuprate **2** to C-3 of the α face of the enones **7a** and (*S*)-**7b**.

Additional corroboration of the dictates of this remarkable finding with the *dl* materials was obtained with the individual enantiomers of the cuprates **2** and the enones **7a** and **7b**. The optically active *cis*-iodovinylcarbinols **11a** ($[\alpha]_D$ −47° (*c* 3.0, CH_3OH)) and **12a** ($[\alpha]_D$ +45° (*c* 3.0, CH_3OH)) were prepared from the respective acetylenic carbinols **13** ($[\alpha]_D$ −21° (*c* 1.0, Et_2O))[12] and **14** ($[\alpha]_D$ + 20° (*c* 1.0, Et_2O)).[13] The divinyl cuprates derived from **11b** and **12b** were allowed to react with enone **7a** to give the enantiomers **15a** and **8a**, respectively. Hydrolysis of **15a** gave **15b**, mp 54.5–55.5°, $[\alpha]_D$ +82° (c 0.81, CH_3OH), $[\Phi]_{312}$ +5750°, $[\Phi]_{276}$ −6280°. Hydrolysis of **8a** gave **8b**, mp 54–55°, $[\alpha]_D$ −75° (*c* 1.0, CH_3OH), $[\Phi]_{312}$ −5540°, $[\Phi]_{276}$ +5670°.[14]

The cuprates from **11b** and **12b** when allowed to react with **7b** gave the enantiomers **16a** and **10a**, respectively.[15]

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(3) To our knowledge, this is the first application of a diimide reduction of an iodoacetylene.

(4) A small amount of the primary iodide **5** (*ca.* 5% from overreduction) was conveniently removed by treatment of the crude hydrolysis product with 40% aqueous dimethylamine for 16 hr at 20° and subsequent extraction with 4 *N* HCl.

(5) Satisfactory combustion analysis was obtained.

(6) The difference in chemical shift of the olefinic protons in **3a** is not sufficiently large enough to allow for a reliable assignment of the coupling constant. The corresponding trans isomer of **3c** showed a coupling of 13 Hz.

(7) The stereochemical integrity of the olefin is expected to be maintained in the cuprate and in the product of conjugate addition. See, for example: F. Näf and P. Degen, *Helv. Chim. Acta*, **54**, 1939 (1971).

(8) F. S. Alvarez, D. Wren, and A. Prince, *J. Amer. Chem. Soc.*, **94**, 7823 (1972).

(9) We estimate from tlc studies using the 13-trans-15α and -15β epimeric alcohols[2] as models that we could have detected a 2% yield of the 13-cis-15α epimer. See also ref 10.

(10) A benzene solution of *dl*-**8a** and diphenyl disulfide was irradiated under an inert atmosphere with 300-nm light to *ca.* 70% conversion to *dl*-**9a**. Isolation by chromatography afforded *dl*-**9a** (*ca.* 40% isolated yield) which was identical with an independently prepared sample[2,8] by tlc and vpc. The isolated *dl*-**9a** was hydrolyzed to the acid *dl*-**9b** which was identical with an independently prepared sample[2,8] by tlc and mixture melting point. The *absence* of 11-desoxy-PGE$_1$ methyl ester[2,8] in the irradiation mixture provided additional evidence that the conjugate adduct *dl*-**8a** was homogeneous, and thereby eliminated the possibility that the 13-cis-15α and -15β diastereomers could possess identical chromatographic properties.

(11) The α and β faces of the enones refer to the bottom and top faces of the cyclopentenones, **7**, as drawn in the structural diagrams.

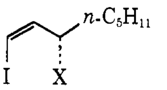
(12) J. Fried, C. H. Lin, M. M. Mehra, and P. Dalven (*Ann. N. Y. Acad. Sci.*, **180**, 38 (1971)) give $[\alpha]_D$ −19.8°.

(13) R. Pappo, P. Collins, and C. Jung (*ibid.*, **180**, 64 (1971)) give $[\alpha]_D$ +20.5°.

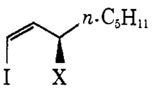
(14) Combination of equimolar amounts of **15b** and **8b** gave the racemate *dl*-**8b**, mp and mmp 75.5–76.5°.

(15) When 3 equiv of *dl*-**2** was allowed to react with 1 equiv of **7b**, no unreacted hydroxyenone **7c** was detected in the product mixture after acid work-up. However, reaction of 3 equiv of the enantiomeric cuprate from **12b** and 1 equiv of **7b** led to *ca.* 30% (60% theory) recovery of unreacted hydroxyenone **7c**. After extensive purification, we obtained a small amount of an oil, $[\alpha]_D$ *ca.* −23° (*c* 0.22, CH_3OH), $[\Phi]_{266}$ −2000°, $[\Phi]_{224}$ +2020°. The observed negative Cotton effect is in complete accord with our expectations for the 4-(*S*)-hydroxyenone (i). In a related cyclopentenone model system (PGA$_1$) a positive Cotton effect has been correlated with the configuration at C-12. See: O. Korver, *Recl. Trav. Chim. Pays-Bas*, **88**, 1070 (1969). Dr. R. Pappo has also assigned the 4-(*S*)-stereochemistry to i ($[\alpha]_D$ −17°), which was

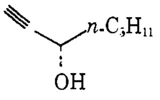
Enzymatic hydrolysis[2] of **16a** gave **16b**, mp 84.5–85.5°, $[\alpha]_D$ +90° (*c* 0.48, CH_3OH), $[\Phi]_{312}$ +6100°, $[\Phi]_{272}$ −5340°[16] Enzymatic hydrolysis[2] of **10a** gave **10b**, mp 84–85°, $[\alpha]_D$ −81° (*c* 0.41, CH_3OH), $[\Phi]_{312}$ −5630°, $[\Phi]_{272}$ +4880°.[16,17]



11a, X = OH
b, X = $OC(CH_3)_2OCH_3$



12a, X = OH
b, X = $OC(CH_3)_2OCH_3$



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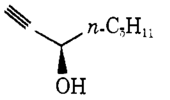
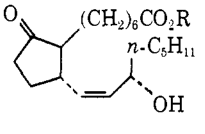
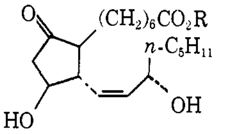


14



15a, R = CH_3
b, R = H



16a, R = CH_3
b, R = H

There are two points of striking contrast when comparing the conjugate additions of the two cuprates **1** and **2**. Firstly, the yields obtained with the cis reagent **2** are very much higher than those obtained with the trans reagent **1**. For example, a 27% yield of 1,4 addition was obtained from **7a**[2] with a threefold excess of reagent **1**, whereas equivalent quantities of **2** and **7a** gave a 60% yield of conjugate addition product.[18] Secondly and indeed the most interesting contrast is found in the high degree of stereoselectivity obtained with the cis reagent. While reaction of trans reagent **1** with **7a** gave a 45:55 mixture of 15α and 15β diastereomers,[2] the cis reagent **2** gave only the 15β diastereomer.[9] Obviously, one diastereomeric transition state (that for the 15β product) is specifically favored in the case of the cis reagent. The net effect of this remarkable result is that we have achieved an asymmetric induction in which the newly created asymmetric center is three carbons removed from the locus of the original asymmetry. We are continuing our investigations in order to elucidate the underlying reasons for this stereoselectivity; an attractive possibility is that coordination of the C-15 oxygen (prostaglandin numbering) with copper would produce a planar reagent with restricted rotation about the C-14–C-15 bond, thereby favoring regiospecific attack on the enone through a coordinated intermediate.

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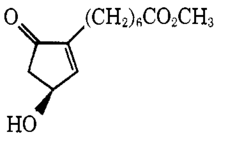
obtained by resolution of racemic i. We wish to thank Dr. Pappo for informing us of this result prior to publication.



i

(16) In the *E*-series prostaglandins the sign of the Cotton effect has been correlated with the configuration at C-8 (see O. Korver, ref 15). Thus, the natural series (8-*R*) exhibit negative Cotton effects and the retro series (8-*S*) exhibit positive Cotton effects. The Cotton effects observed with the 11-desoxy-13-cis compounds **8b** and **15b** are also consistent with this correlation. For compounds **10b** and **16b**, the absolute configuration at C-15 is determined by the asymmetric organocopper reagent and the configuration at C-8 is derived from the sign of the Cotton effect. The trans–trans configuration assigned to the two remaining asymmetric centers is predicted from the method of synthesis and is corroborated by the successful use of this method in the synthesis of (−)-PGE_1.[2]

(17) Combination of equimolar amounts of enantiomers **16b** and **10b** gave the racemate *dl*-**10b**, mp and mmp 87.0–87.5°.

(18) Others have observed slightly higher yields with cis reagents; see ref 7.

(19) Syntex Postdoctoral Fellow, 1971–1972.

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Received August 21, 1972

Conformational Effects in the Electron Paramagnetic Resonance Spectra of Cyclohexanonyl Radicals in Adamantane

Sir:

Several authors have reported observation of conformational effects in the epr spectra of free radicals derived from cyclohexane. For example, Ogawa and Fessenden[1] studied the spectrum of the cyclohexyl radical in solid cyclohexane between 188 and 273°K and observed alternating line width effects[2] which were attributed to interconversions between the two chair forms of the radical with an activation energy of 4.9 kcal/mol. Similar effects have been noted in spectra of radicals derived from piperidine[3] and dioxane[3,4] and, more recently, in semidione[5] and cyclohexenone[6] radical anions. Consideration of these results reveals that the amount of information which can be obtained regarding structure and conformation of free radicals containing six-membered rings is in direct proportion to the temperature range over which they can be studied. For this reason, we wish to report here preliminary results on a series of cyclohexanonyl radicals trapped in adamantane which illustrate the versatility of this technique[7] for epr studies over a wide temperature range and provide valuable new information on the properties of β-carbonyl radicals.

Cyclohexanonyl radicals are produced by room temperature X-irradiation of a solid pellet of carefully purified adamantane containing a small amount of deliberately added ketone and are studied using a Varian E-4 spectrometer equipped with a variable temperature controller. The radicals are formally obtained by removal of a hydrogen atom from the C-2 position; for example, X-irradiation of cyclohexanone yields the radical I which undergoes conformational interconversions between the two half-chair forms A and B.

Selective line broadening is observed when the interacting β protons (H_a and H_b) experience different magnetic environments at a rate which is comparable to the difference in hyperfine splitting constants (hfsc) in the two sites (pseudoaxial and pseudoequatorial).[8] Figure 1a illustrates this phenomenon for the radical obtained from cyclohexanone in adamantane-d_{16}. At

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(1) S. Ogawa and R. W. Fessenden, *J. Chem. Phys.*, **41**, 994 (1964).

(2) For a review, see P. D. Sullivan and J. R. Bolton, *Advan. Magn. Resonance*, **4**, 39 (1970).

(3) W. T. Dixon and R. O. C. Norman, *J. Chem. Soc.*, 4850 (1964).

(4) H. Zeldes and R. Livingston, *J. Chem. Phys.*, **45**, 1946 (1966).

(5) G. A. Russell, G. R. Underwood, and D. C. Lini, *J. Amer. Chem. Soc.*, **89**, 6636 (1967).

(6) I. H. Elson, T. J. Kemp, and T. J. Stone, *ibid.*, **93**, 7091 (1971).

(7) D. E. Wood and R. V. Lloyd, *J. Chem. Phys.*, **52**, 3840 (1970); **53**, 3932 (1970).

(8) E. L. Eliel, *et al.*, "Conformational Analysis," Interscience, New York, N. Y., 1965, Chapter 2.