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CONFIGURATIONAL STABILITY OF ALLENIC ANIONS, USE OF A VITAMIN D DERIVED CD FRAGMENT AS A STEREOCHEMICAL PROBE AND THE STEREOSELECTIVE SYNTHESIS OF PRECURSORS

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Summary: Metallation (n-BuLi, t-BuOK, THF) followed by quenching (DCl, D₂O) of (S)-allenes 4a-c occurs primarily with retention of configuration, whereas that of (R)-allenes 4d-e occurs mainly with inversion; the allenes 4 were prepared from related propargyl alcohols (5, 7.9).

Recently, in connection with vitamin D studies, we made the unusual observation that metallation (tert-butyllithium, ether, -78 to -55 °C) of 1 followed by quenching of the resultant allenyllithium species with a suitable electrophile affords 2 and 3 in ratios as high as 13.5 to 1. In order to better understand the origin of this remarkable diastereoselectivity, we have undertaken a study of the configurational behavior of allenic anions^{2,3} derived from several epimeric substituted allenes such as 4, which in this instance are related to the CD fragment of vitamin D.^{1,4-5} This particular CD fragment constitutes an excellent stereochemical probe,



because the ¹H-NMR chemical shift of the C₁₈ angular methyl group is sensitive to the orientation of the C2, substituent (i.e., 2 vs. 3). It is the purpose of this communication to report on the stereoselective syntheses of 4 and on studies concerning their derived anions.

To study the metallation, the allenes 4 were treated under several reaction conditions with strong base and then quenched with 1 \underline{M} DCl in D₂O (or 1 \underline{M} HCl in H₂O in the case of deuterated allene 4b) (see Table I). Using tert-butyllithium as base and THF as solvent 6 (40 min, RT), we observed ~90% metallation of 4a (entry 1) and ~50% metallation of 4d (entry 5). Under identical conditions, no significant metallation of the tert-butyl substituted allenes 4c and 4e was observed. These results led us to change to the stronger base system, the Lochmann-Schlosser complex, n-BuLi/t-BuOK, in THF. 7 Treatment of the allenes 4a-c (entry 2, 3 and 4) and 4d (entry 6) with 1.1 eq t-BuOK and 1.2 eq n-BuLi in THF at -78 °C for 2 h, followed by quenching with dilute mineral acid resulted in >98% metallation, as indicated by ¹H-NMR spectroscopy.⁵ Under these conditions, allene 4e was not completely metallated (entry 7). However, at a higher temperature (-50 °C, 1h), >98% reaction occurred as indicated by the extent of deuterium incorporation (entry 8). Most interesting, however, is the stereochemical course of these metalla-

Entry	Starting Material	Starting Material R:S ^a	Product R:S ^a	D (or H) Incorporation (%) <u>b</u>	Yield (%)	Reaction Conditions
1 2 3 4 5 6 7 8	4a 4b 4c 4d 4d 4d 4d 4e 4e	7:93 8:92 7:93 5:95 95:5 100:0 100:0 100:0	15:85 4:96 14:86 7:93 57:43 8:92 56:44 7:93	∿90 >98 >98 >98 ∿50 >98 ∿50 >98	93 97 92 89 78 95 87 81	0 व 0 व 0 म

TABLE I. Metallation Studies of 4a-e

^ADetermined by ¹H-NMR spectroscopy by integrating the peaks assigned to the C₁₈ angular methyl group (see Footnote 5). ^bDetermined by ¹H-NMR with vitamin D₃ as an internal standard (see Footnote 5). ^Ctert-BuLi, THF, -78 °C, 5 min; r.t., 45 min; 1 M DCl in D₂O, -78 °C; r.t., 1 h; workup and analysis. ^dt-BuOK, n-BuLi, THF, -78 °C, 2 h; 1 M DCl in D₂O, -78 °C; r.t., 1 h; workup and analysis. ^et-BuOK, n-BuLi, THF, -78 °C, 1 h; 1 M HCl in H₂O, -78 °C; r.t.; workup and analysis. ^ft-BuOK, n-BuLi, THF, -78 °C, 5 min; -50 °C, 1 h; 1 M DCl in D₂O, -78 °C; r.t., 1 h; workup and analysis.

tions. As shown in Table I, the (S)-allenes 4a-c (entries 1-4) undergo this reaction with retention of configuration, while the (R)-allenes 4d-e (entries 5-8) exhibit almost complete inversion. A most simple explanation of these observations is that alkyl substituted allenic anions, unlike α -chloroallenic anions, ³ are configurationally unstable. While it <u>must be emphasized</u> that the alkyl and chloro substituted allenic anions were generated under quite different conditions, this order in configurational stability is in accord with Wilmshurst and Dykstra's recent theoretical calculations^{2a} as well as with the well known effect of electronegative substituents on barriers to inversion of amines.⁸ It would be worthwhile to systematically compare a series of substituted allenic anions under a set of identical reaction conditions, however. As to why the alkali metal derivative of the allenes 4 produce primarily only (S)-allenes upon quenching remains to be answered. At least one aspect of the problem concerns the structure of the allenic anion, which, <u>as discussed earlier</u>, ^{1a} is unlikely to possess a linear three carbon geometry (either planar or allenelike in geometry), but rather, some pyramidal character must be associated with the propargylic terminus.¹

The syntheses of the various allenes 4^9 are presented in Scheme I, which summarizes yields [in brackets] as well as diastereomeric purities (in parentheses; estimated by ¹H-NMR spectroscopy⁵) where relevant. While Scheme I is self-explanatory, several features of the stereochemical data are worth noting, especially in view of earlier reports on analogous reactions, which have created some confusion in the literature. Firstly, the formation of 4a and 4b from 5a, 4c from 5b, and 4d from 9 by reaction of a propargylic alcohol^{1a,4} with 1:3 AlCl₃-LiAlH₄ (or deuteride) is indicative of a preferred anti-displacement of the leaving group. This is surprising in view of a number of literature reports, ¹⁰ suggesting the preference for syn products. It should be noted, however, that Borden and Corey in their original synthesis of optically active 1,3-ditert-butylallene, ^{11a} using such an allene forming reaction, concluded it to be an <u>anti</u>-displace-



SCHEME I. <u>Reagents</u>: <u>AphSCl</u>, Et₃N (2 eq), CH₂Cl₂, -78 °C, 2 h; r.t., 1 h. <u>b</u>LiAlH₄, AlCl₃ (3:1), THF, reflux, 16 h. <u>c</u>LiAlD₄, AlCl₃ (3:1), THF, reflux, 16 h. <u>d</u>CH₃Li, Et₂O, -78 °C, 10 min. <u>e</u>Reference 4 of text. <u>f(tert-Bu)</u>₂Cu(CN)Li₂, Et₂O, -78 °C, 6 h; r.t., 1 h. <u>Gn-BuLi</u>, THF, -78 °C, 5 min; r.t., <u>30</u> min. <u>h(CH₃)</u>₃Sicl, -78 °C, 5 min; r.t., 1 h. <u>i</u>CH₃I, -78 °C, 5 min; r.t., 30 min. <u>j(n-Bu)</u>₄NF, THF, r.t., 1 h.

ment, which has recently been confirmed by Koreeda using X-ray techniques.^{11b} In addition, another X-ray study revealed very recently the same in a steroid case.^{11c} Secondly, the transformations 7 to 4e and 8b to 4c using (tert-Bu)₂Cu(CN)Li₂,¹² like the previously reported⁴ conversions of 7 and 8b to 4d and 4a, respectively, also proceed with <u>anti</u>-selectivity. These results taken together with the recent X-ray structure in a steroid case^{11c} further emphasize that all cuprate mediated alkylative conversions of propargylic systems to allenes reported to date proceed with <u>anti</u>-selectivity. Finally, it should be mentioned that the propargyl alcohol + allenic sulfoxide + hydrocarbon sequence (eq., 5a + 6a + 4d, 5b + 6b + 4e and 9 + 10 + 4a) has <u>Acknowledgments</u>. We are grateful to the National Institutes of Health (USPHS Grant AM-16595) for financial support. Dr. Menso P. Rappoldt of Duphar B.V. (Weesp, the Netherlands) provided generous samples of vitamin D_3 used in the preparation of the various C/D fragments. We also thank the NSF Midwest Center for Mass Spectroscopy for mass spectra, the Netherlands Organization for the Advancement of Pure Research (ZWO) for a partial stipend to EMGAvK and the Gran Mariscal de Ayacucho Foundation (Venezuela) for a graduate fellowship for AH.

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- 5. Analyses were carried out by ¹H-NMR spectroscopy. The diastereomeric ratios were determined by integrating the peaks assigned to the C_{18} angular methyl groups of epimeric mixtures of 4. Pertinent chemical shifts include: 4a, $\delta 0.66$ (C_{18} -CH₃, s) and 5.02 (H₂, m); 4d, $\delta 0.60$ (C_{18} -CH₃, s) and 5.02 (H₂, m); 4c, $\delta 0.68$ (C_{18} -CH₃, s) and 5.06 (H₂, m); 4e, $\delta 0.61$ (C_{18} -CH₃, s) and 5.04 (H₂, m). Deuterium content was determined by adding a near equimolar amount of the internal standard, vitamin D₃, for which the C_{18} -CH₃ appears at $\delta 0.54$ and H₃ (the hydrogen on carbon bearing the hydroxyl) at $\delta 3.94$ [Wing, R.M.; Okamura, W.H.; Rego, A.; Pirio, M.R.; Norman, A.W. J. Am. Chem. Soc. 1975, 97, 4980]. Integration of the signals due to the allenic hydrogen of 4 relative to H₃ of an equimolar amount (by normalizing the C_{18} -methyl integrals of the allene 4 and the standard) of vitamin D₃ provided a convenient measure of the deuterium content.
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