crystalline, air-stable, hydrochloride salt by the following procedure. Diphenylphosphine[3] (28.0 mL, 29.6 g, 160 mmol) was added by syringe to a suspension of potassium *tert*-butoxide (28 g, 250 mmol) in 500 mL of dry THF under argon. The resulting deep red solution was stirred for 5 min and bis(2-chloroethyl)amine hydrochloride (14.3 g, 80 mmol) added as a coarse powder.[4] The mixture was refluxed for 16 h, poured into 800 mL of hexane, and washed in succession with 300-mL portions of 10% aqueous NaOH and saturated aqueous NaCl solutions. The hexane layer was separated, filtered, and stirred vigorously with 800 mL of 2 N aqueous HCl solution giving a dense white precipitate of **1** HCl. Recrystallization from 300 mL of boiling acetonitrile gave a 90% yield (34.4 g) of fine white needles, mp 174.5–175.5 °C.[5,6]

Acylation of **1** was accomplished by a number of the procedures commonly used for the formation of amides (Table I). Isocyanates and carboxylic acid chlorides, anhydrides, and active esters appear to react cleanly with the nitrogen atom of **1**. Sulfonyl chlorides and cyanogen bromide give complex product mixtures: no N-functionalized derivatives of **1** have been isolated from these reactions. D-Gluconic acid δ-lactone, *O*-alkylisouronium bromides, and *S*-alkylisothiouronium bromides were unreactive toward **1**. A representative procedure is that for *N,N*-bis(2-diphenylphosphinoethyl)biotinamide (**9**). The *N*-hydroxysuccinimide active ester of *d*-biotin[7] (67 mg, 0.20 mmol), **1** HCl (95 mg, 0.20 mmol), and triethylamine (80 mg, 0.80 mmol) were added to 3 mL of degassed DMF. The reaction mixture was stirred at room temperature for 60 h under argon, slowly diluted with 8 mL of water, and cooled to 4 °C. The resulting white precipitate was collected, washed with water, and dried (0.3 Torr), yielding 112 mg of **9** as a waxy solid.[8] Other compounds in Table I were also prepared using unexceptional procedures.

The range of structural types represented in Table I attests to the generality of this method of preparing phosphines appropriately functionalized for specific uses. Compounds **3** and **9** introduce diphosphine ligands into proteins (carbonic anhydrase[9] and avidin[10]) by noncovalent binding; **4** is a water-soluble diphosphine which serves as the basis for water-soluble rhodium-based homogeneous hydrogenation catalysts;[11] the rhodium(I) complex of **7** is an asymmetric hydrogenation catalyst showing modest enantioselectivity (30% enantiomeric excess for hydrogenation of α-acetamidoacrylic acid); **5** is a potential tetradentate phosphine; **8** is a chelating polyphosphine showing interesting surfactant properties in aqueous solutions.

The usefulness of this procedure for diphosphine synthesis rests on four features. First, the formation of amides by acylation of amines is one of the best understood and most general coupling methods in organic chemistry. The fact that it is possible to acylate the secondary amine of **1** without interference by the diphenylphosphine groups makes it possible to utilize this reaction for the preparation of a wide variety of diphosphines. Second, since the preformed diphosphine moiety is introduced as a unit, yields are relatively high. Third, the coupling reaction is compatible with a range of functionalities. Fourth, carboxylic acids and their derived acylating agents are readily available in great variety. We will describe details of the procedures reported here, extensions to other aminopolyphosphines and acylating agents, and applications of the resulting functionalized phosphines in subsequent publications.

References and Notes

(1) Supported by the National Science Foundation, Grants MPS74-20946 and 7711282-CHE.
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(3) R. E. Ireland and D. M. Wells, *Org. Syn.*, **56**, 44 (1977).
(4) *CAUTION:* Bis(2-chloroethyl)amine is a severe irritant and a potential carcinogen.
(5) NMR ($CDCl_3$): δ 2.3–3.3 (m, 8 H), 7.0–7.6 (m, 20 H), 9.9 (s, 2 H). Anal. Calcd for $C_{28}H_{30}ClNP_2$: C, 70.42; H, 6.33; N, 2.93. Found: C, 70.30; H, 6.27; N, 2.90.
(6) Recrystallization is unnecessary for some further uses, but high purity for **1** HCl makes it easier to crystallize difficulty purified derivatives such as **5** and **9**.
(7) This compound was prepared by the method of E. Bayer and M. Wilchek, *Methods Enzymol.*, **34**, 265 (1974); it was recrystallized from acetonitrile with charcoal to mp 213–214 °C.
(8) This substance was typical of those in Table I in being poorly crystalline. Its IR spectrum (Nujol, cm^{-1}) had peaks at 1705 and 1630, and its NMR spectrum showed aryl and biotinyl absorptions. Anal. Calcd for $C_{38}H_{43}N_3O_2P_2S$: C, 68.35; H, 6.49; N, 6.29. Found: C, 68.34; H, 6.40; N, 5.99.
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(11) R. Nuzzo, M. Wilson, and G. M. Whitesides, unpublished work; D. Feitler, Ph.D. Thesis, Massachusetts Institute of Technology, Cambridge, Mass., 1977.
(12) Predoctoral trainee: NIH 5 T32 CA 09112 CT.

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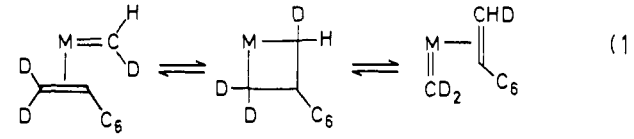
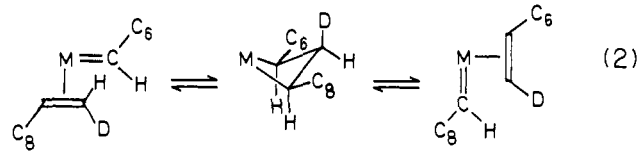
Stereochemistry of the Degenerate Metathesis of Terminal Alkenes—the Nature of the Chain-Carrying Metal–Carbene Complex

Sir:

The recent demonstration that the transition metal catalyzed metathesis of alkenes proceeds by a nonpairwise process[1] is most readily explained by a mechanism involving the equilibration of a metal-carbene-alkene complex with a metallacyclobutane.[2] The degenerate metathesis of terminal alkenes has been demonstrated with deuterium labeled alkenes[3] and was found to be much more rapid than productive metathesis which yields ethylene and an internal alkene. A priori, there are two explanations which can account for the degenerate metathesis of terminal alkenes. (1) The reaction may proceed





via a M=CH_2-carbene complex which reacts selectively with a terminal alkene to transfer the most substituted alkylidene unit and to regenerate a M=CH_2-carbene complex. Such a selectivity could be attributed either to steric preferences or to electronic stabilization of a negatively polarized carbene ligand, $M^+—C^-H_2$. (2) Alternatively, the reaction may proceed via a M=CHR complex which reacts selectively with a terminal alkene to transfer the least substituted alkylidene unit and to regenerate a M=CHR-carbene complex. Such a selectivity could be attributed to electronic stabilization of a positively polarized carbene ligand, $M^-—C^+HR$.

Model studies with isolated carbene complexes have led to

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Table I. Stereochemistry of the Degenerate Metathesis of $C_6H_{13}CH{=}CD_2$ and (Z)-$C_8H_{17}CH{=}CHD$

Catalyst system	Ref	% octene-d_1	(Z)-C_6H_{13}-$CH{=}CHD$[15] / (E)-C_6H_{13}-$CH{=}CHD$
$MoCl_2(NO)_2(PPh_3)_2$, $(CH_3)_3Al_2Cl_3$	16	6.3	2.3
$C_6H_5WCl_3$, $AlCl_3$	7	9.5	1.7
WCl_6, $(CH_3)_4Sn$	5b	6.3	1.5
$W(CO)_5(PPh_3)$, $CH_3CH_2AlCl_2$, O_2	17	10.9	1.3
$Re(CO)_5Cl$, $CH_3CH_2AlCl_2$	18	5.1	2.4

opposite results for oppositely polarized carbene complexes. The reaction of the electrophilic carbene complex $(CO)_5WC(C_6H_4\text{-}p\text{-}CH_3)_2$[4] with alkenes led to the selective transfer of the least substituted alkylidene unit of a terminal alkene to the diarylcarbene and provides a good model for reaction sequence 2. The reaction of the nucleophilic carbene complex $(C_5H_5)Cl_2Ta{=}CHC(CH_3)_3$[5] with propene gives 95% $(CH_3)_3CCH_2C(CH_3){=}CH_2$ which can be explained in terms of reaction sequence 1.[6]

To distinguish between these two possible polarizations of the chain-carrying metal-carbene complex in olefin metathesis, we have studied the metathesis of mixtures of $CD_2{=}CHC_6H_{13}$ and (Z)-$CDH{=}CHC_8H_{17}$. If the reaction proceeds via sequence 1, the ratio of (Z)- to (E)-$CHD{=}CHC_6H_{13}$ should be 1:1 since neither the metal-carbene-alkene complex (I) nor the metallacyclobutane (II) are capable of retaining stereochemical information. However, if terminal olefin degenerate metathesis proceeds via reaction sequence 2 both III and IV retain stereochemical information; a preference for retention of stereochemistry would be expected since the reaction should proceed through the more stable puckered metallacyclobutane.[9]

The metathesis of a 1:1 mixture of (Z)-1-decene-$1\text{-}d_1$[10] and 1-octene-$1,1\text{-}d_2$[11] in chlorobenzene was carried out by injection of a catalyst solution containing $MoCl_2(NO)_2(PPh_3)_2$ and methylaluminum sesquichloride (MASC) (total olefin:Mo:MASC, 85:1:15).[9b] After 9 min, the solution was quenched with absolute ethanol and GC analysis revealed ~0.7% productive metathesis ($C_{14}H_{28}$, $C_{16}H_{32}$, $C_{18}H_{36}$). The reaction mixture was bulb to bulb distilled under high vacuum and epoxidized using *m*-chloroperoxybenzoic acid.[12] The reaction mixture was washed with $NaHSO_3$ and $NaHCO_3$ solutions and concentrated under reduced pressure (14 mm, 30 °C). The epoxides of 1-octene and 1-decene were separated from the residue by preparative gas chromatography (10% UCW-98, 110 °C, pretreated with hexamethyldisilazane). In the 270-MHz FT ^1H NMR spectra of the isolated 1-octene epoxides,[13] (Z)-1-octene-$1\text{-}d_1$ oxide gives rise to a doublet at δ 2.73 (J = 4 Hz), (E)-1-octene-$1\text{-}d_1$ oxide gives rise to a doublet at δ 2.45 (J = 2.8 Hz), and 1-octene-$1,1\text{-}d_2$ oxide (Figure 1) gives no signal in these regions. Integration of the spectrum indicated a 94:6 mixture of dideuterio and monodeuterio material. The ratio of (Z)- to (E)-1-octene-$1\text{-}d_1$ oxide was 2:1.[14] The results for other olefin metathesis catalysts are given in Table I.

The observation that terminal alkene metathesis is stereospecific with retention of configuration is consistent with M=CHR being the chain-carrying carbene complex in degenerate metathesis. The observed stereochemical result is consistent with a $M{=}CH_2$ intermediate only if (1) the metathesis catalyst is asymmetric and requires preferential formation of the metal-alkene complex and (2) there is a substantial barrier to rotation about the M=CHD bond. Asymmetric metathesis catalysts have been suggested by Basset[9e] to explain the retention of stereochemistry observed in the metathesis of internal alkenes. Barriers to rotation about the

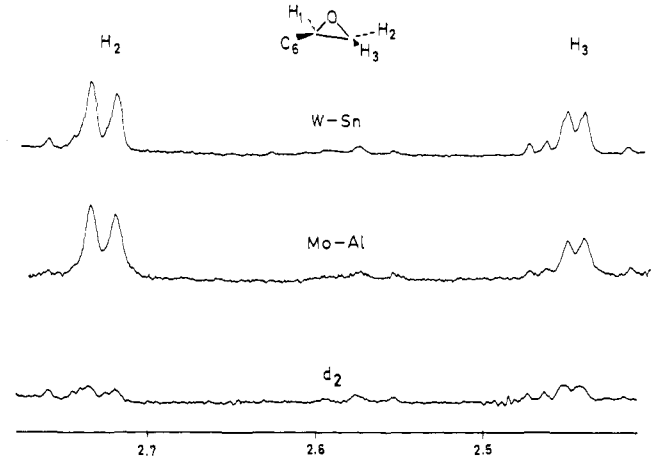
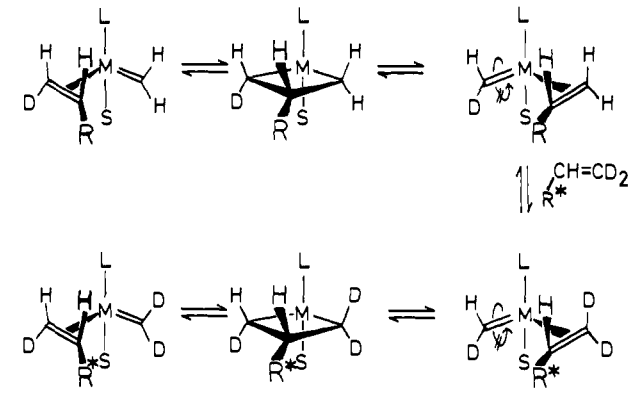


Figure 1. 270-MHz ^1H FT NMR spectrum of 1-octene oxide from 650 to 750 Hz relative to Me_4Si: bottom, 1-octene-$1,1\text{-}d_2$ oxide starting material; middle, 1-octene oxide isolated from the metathesis reaction using $MoCl_2(NO)_2(PPh_3)_2/(CH_3)_3Al_2Cl_3$ as the catalyst; top, 1-octene oxide isolated from the metathesis reaction using $WCl_6/(CH_3)_4Sn$ as the catalyst.



carbene metal bond in $(C_5H_5)(C_5H_4CH_3)Ta(CH_3)CH_2$[19] and related conplexes have been observed but may be relevant only in special systems such as the $(C_5H_5)_2M{=}CH_2$ system in which there is a single localized metal orbital which can π bond to the carbene ligand.[20] While the present results favor a M=CHR intermediate in degenerate metathesis, clearly ambiguities remain.

Acknowledgment. We gratefully acknowledge the support of this work by the National Science Foundation.

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(6) Gassman[7] has reported that ethylcyclopropane reacts with terminal alkenes ($RCH{=}CH_2$) in the presence of a known metathesis catalyst ($C_6H_5WCl_3/AlCl_3$ in C_6H_5Cl) to give significant amounts of $CH_3CH_2CH{=}CHR$ and he has interpreted this as support for reaction sequence 1. However, Mango[8] has advanced thermodynamic arguments against the relationship between the ring opening of cyclopropanes and olefin metathesis.
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(9) At this point, it is not clear whether a diequatorial or a diaxial substituted

metallocyclobutane is preferred. For purposes of these arguments, a preference for either conformation would lead to retention of stereochemistry in degenerate metathesis. For discussions of the stereochemistry of the metathesis of internal alkenes, see (a) J. Wang and H. R. Menapace, *J. Org. Chem.*, **33**, 3794 (1968); (b) W. B. Hughes, *Chem. Commun.*, 431 (1969); (c) J. M. Basset, J. L. Bilhou, R. Mutin, and A. Theolier, *J. Am. Chem. Soc.*, **97**, 7376 (1975); (d) C. P. Casey, L. D. Albin, and T. J. Burkhardt, *ibid.*, 99, 2533 (1977); (e) J. L. Bilhou, J. M. Basset, R. Mutin, and W. F. Graydon, *ibid.*, **99**, 4033 (1977).
(10) Prepared by hydroalumination of 1-decyne-*1-d*$_1$ followed by H_2O quench. The decene was further purified by treatment with 5% ethanolic $AgNO_3$ to remove alkynes which were found to inhibit olefin metathesis.
(11) Prepared by $LiAlD_4$ reduction of ethyl caprylate, conversion of the resulting deuterated octanol to octyl formate and pyrolysis of the formate at 530 °C.
(12) The epoxidation of (*Z*)-1-decene-*1-d*$_1$ with *m*-$ClC_6H_4CO_3H$ was shown to be >99% stereospecific.
(13) GC analysis of the NMR sample indicated <0.1% 1-decene oxide.
(14) (a) Integrals of the oxirane protons were determined by planimetry. (b) The relative amount of monodeuterio oxide was determined by measuring for each NMR the ratio of protons in positions 1 and 2. The estimated error in the ratio of monodeuterated products is ±0.1. (c) In the 270-MHz FT NMR experiment the number of transients was limited to prevent imminent overflow during data collection. Thus all data were collected using the maximum number of bits to ensure maximum time domain range. (d) In a separate experiment a 99.9-s pulse delay was used in obtaining the 270-MHz FT NMR spectrum to ensure that this ratio was not caused by a significant difference in T_1's for the two isomers.
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(21) Proctor & Gamble Predoctoral Fellow.

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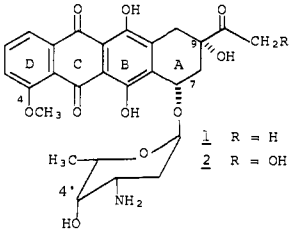
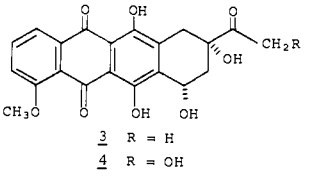
Total Synthesis of Adriamycinone. Regiospecific Synthesis of Anthracyclinones via Base-Catalyzed Cyclizations

Sir:

The anthracycline antibiotics, daunorubicin (**1**) and especially adriamycin (**2**), are widely used for the treatment of a



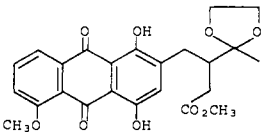
1 R = H
2 R = OH



3 R = H
4 R = OH

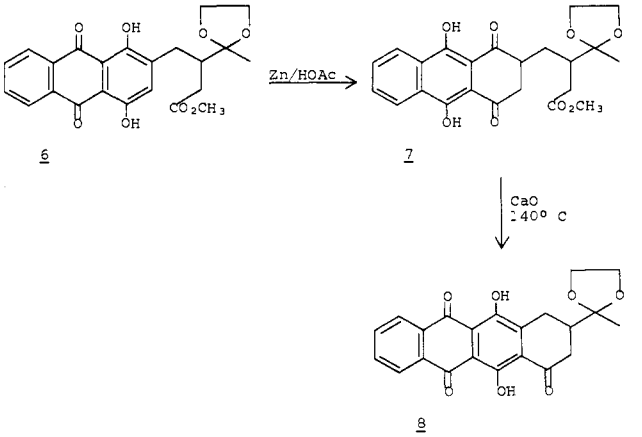
variety of human cancers.[1] Total syntheses of the aglycone (anthracyclinone) portion of these antibiotics have been a topic of considerable interest in recent years owing to the lack of an efficient biosynthetic process[2] and epimerization of the C-4′ hydroxyl in daunosamine[3] that may result in analogues with apparent reduced cardiotoxicities. Although several synthetic approaches to (±)-daunomycinone (**3**) or (±)-adriamycinone (**4**) have already been described,[4-6] invariably these routes require the separation of regioisomers (orientation of rings A and D substituents) at some stage. Notable exceptions are the BA → DCBA schemes of Kende[7] and Swenton.[8] Herein, we disclose a fundamentally different regiospecific synthesis of anthracyclinones from an appropriately substituted anthraquinone derivative. The construction of the alicyclic A ring was achieved via intramolecular Marschalk- and Claisen-type condensations.

Retrosynthetic analysis of the anthracyclinone molecule reveals that **5** could serve as a plausible precursor, but the



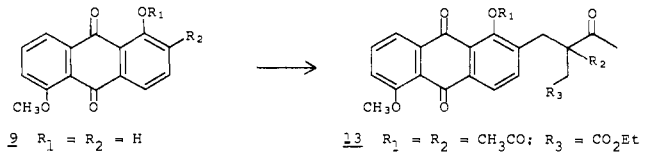
5

success of this approach is dependent on the availability of a suitable method for ring A closure. Owing to the strong electron-withdrawing property of the anthraquinone system, **5** resisted cyclization when treated with a variety of conventional strongly acidic or basic reagents.[9] A possible solution to this recalcitrant problem was indicated in our recent model studies.[9] The substituted anthraquinone, **6**, was first transformed into its leuco form, **7**, which underwent cyclization under the



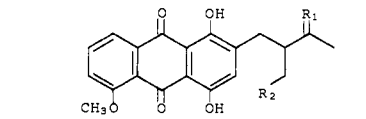
6 **7** **8**

following rigid experimental condition: CaO or BaO as base, Zn as reducing agent to suppress back-oxidation of **7** to **6**, and ethylene glycol as solvent.[10] The successful development of this model ring closure reaction[11] prompted us to turn our attention to the synthesis of **5**. Marschalk methylation[12] of 1-hydroxy-5-methoxyanthraquinone[13] (**9**) gave **10**,[14] mp 185-186 °C, in 60% yield. After quantitative conversion of **10** into **11** (Ac_2O, H_2SO_4, 3 h), mp 195-197 °C, **11** was treated with 1.3 equiv



9 $R_1 = R_2 = H$
10 $R_1 = H$; $R_2 = CH_3$
11 $R_1 = Ac$; $R_2 = CH_3$
12 $R_1 = Ac$; $R_2 = CH_2Br$

13 $R_1 = R_2 = CH_3CO$; $R_3 = CO_2Et$
14 $R_1 = R_2 = H$; $R_3 = COOH$



15 $R_1 = O$; $R_2 = COOH$
16 $R_1 = O$; $R_2 = COOCH_3$
17 $R_1 = OCH_2CH_2O$; $R_2 = COOH$
18 $R_1 = OCH_2CH_2O$; $R_2 = COOCH_2CH_2OH$

of NBS to yield bromide **12** (60%), mp 213-216 °C, which was alkylated (NaH, DMF, 0 °C) with 3-acetyllevulinic acid ethyl ester to afford **13**, mp 181-182 °C, in 96% yield. Hydrolysis of the ester grouping and cleavage of the β-diketone (reverse Claisen) were simultaneously effected by reaction of **13** with 5% aqueous NaOH at 65 °C for 5 h to give **14** (90%), mp 197-200 °C. Elbs oxidation[15] of **14** gave 40% **15**, mp 124-126

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