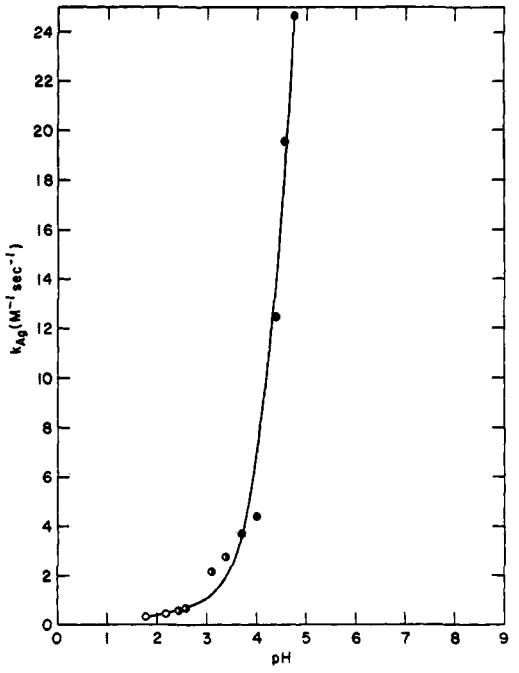
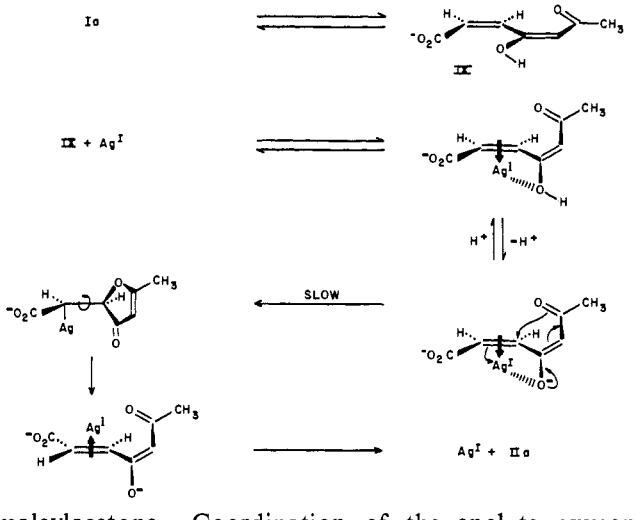


Figure 1. Second-order rate constants for silver(I)-catalyzed cis–trans isomerization of maleylacetone methyl ester (VII) *vs.* pH: closed circles refer to acetate buffers (0.02 *M*); open circles refer to malonate buffers (0.2 *M*); half circles refer to malonate buffers (0.01 *M*). Curve represents calculated values of $k_{obsd} = [k_A^- K + k_{HA}(H^+)]/[K + (H^+)]$, for $K = 10^{-5}$ *M*, as determined by least-squares fitting.

kinetically active species is a complex of silver and the enolate ion of VII.[12] We suggest the following mechanism (Scheme I) for the catalyzed isomerization of

Scheme I



maleylacetone. Coordination of the enolate oxygen with tetrahedral silver facilitates twisting about the C-3–C-4 bond thereby to place the carbonyl oxygen below (or above) the C-1–C-2–C-3–C-4 plane and facilitate nucleophilic attack on the double bond. Isomerization of VI is prevented by the inability of its silver complex to form an enolate ion.

(12) There is no apparent general acid–base catalysis. Rates are essentially the same in 0.02, 0.25, and 0.50 *M* acetate buffers, pH 4.0.

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Angular Alkylation through Intramolecular Carbenoid Insertion. A New Stereocontrolled Route to Synthetic Intermediates to the Diterpene Alkaloids and C_{20}-Gibberellins[1]

Sir:

A crucial problem in the total synthesis of a large number of complex diterpenoids, for example, the *Garrya* and *Atisine* groups of diterpene alkaloids[2] and a few C_{20}-gibberellins,[3] is the introduction of the C-10 functionalized angular carbon residue in combination with the C-4 substituents with appropriate stereochemical control, in a hydrophenanthrene or a hydrofluorene moiety. In spite of the notable achievements in the total synthesis[4] of these compounds there are only a limited number of methods[4,5] for realizing this synthetic task. We present here a new simple synthetic approach which rests in utilizing the carboxyl at C-4 for introduction of the functionalized C-10 substituent in a stereospecific manner in providing some key intermediates toward complex diterpenoids. Our method of angular alkylation is based upon a regioselective intramolecular α-ketocarbenoid insertion across the C-10 benzylic C–H bond in the carbenoid thermal decomposition of the α-diazomethyl ketones **4** and **4a** from the easily accessible[6] 20-nor ring-C-aromatic resin acid analogs **3** and **3a**. We also studied a number of model compounds.[7] For example, the thermal decomposition of a dilute solution of the crude diazoketone **1b** derived from the bridged bicyclo[3.3.1]nonene derivative **1a**,[8] in the presence of anhydrous copper sulfate in tetrahydrofuran, afforded the tetracyclic liquid ketone **2**[9] [$\nu_{max}^{CHCl_3}$ 1740 cm^{-1}; 2,4-dinitrophenylhydrazone, mp 171°] in 53% overall yield from **1a** as the only isolable product after column chromatography.

The crude diazo ketone **4**, prepared from **3**, on treatment with anhydrous copper sulfate in boiling

(1) Presented at the 8th International Symposium on the Chemistry of Natural Products, New Delhi, India, Feb 6–12, 1972.

(2) For a review see: S. W. Pelletier, *Quart. Rev., Chem. Soc.*, 21, 525 (1967).

(3) See: J. R. Hanson, "The Tetracyclic Diterpenes," Pergamon Press, Oxford, 1968, pp 54–56.

(4) (a) W. Nagata, T. Sugasawa, M. Narisada, T. Wakabayashi, and Y. Hayase, *J. Amer. Chem. Soc.*, 85, 2342 (1963); 89, 1483 (1967); (b) W. Nagata, M. Narisada, T. Wakabayashi, and T. Sugasawa, *ibid.*, 86, 929 (1964); 89, 1499 (1967); (c) S. Masamune, *ibid.*, 86, 290, 291 (1964); (d) R. W. Guthrie, W. A. Henry, H. Immer, C. M. Wong, Z. Valenta, and K. Wiesner, *Collect. Czech. Chem. Commun.*, 31, 602 (1966); (e) W. Nagata, T. Wakabayashi, M. Narisada, Y. Hayase, and S. Kamata, *J. Amer. Chem. Soc.*, 93, 5740 (1971).

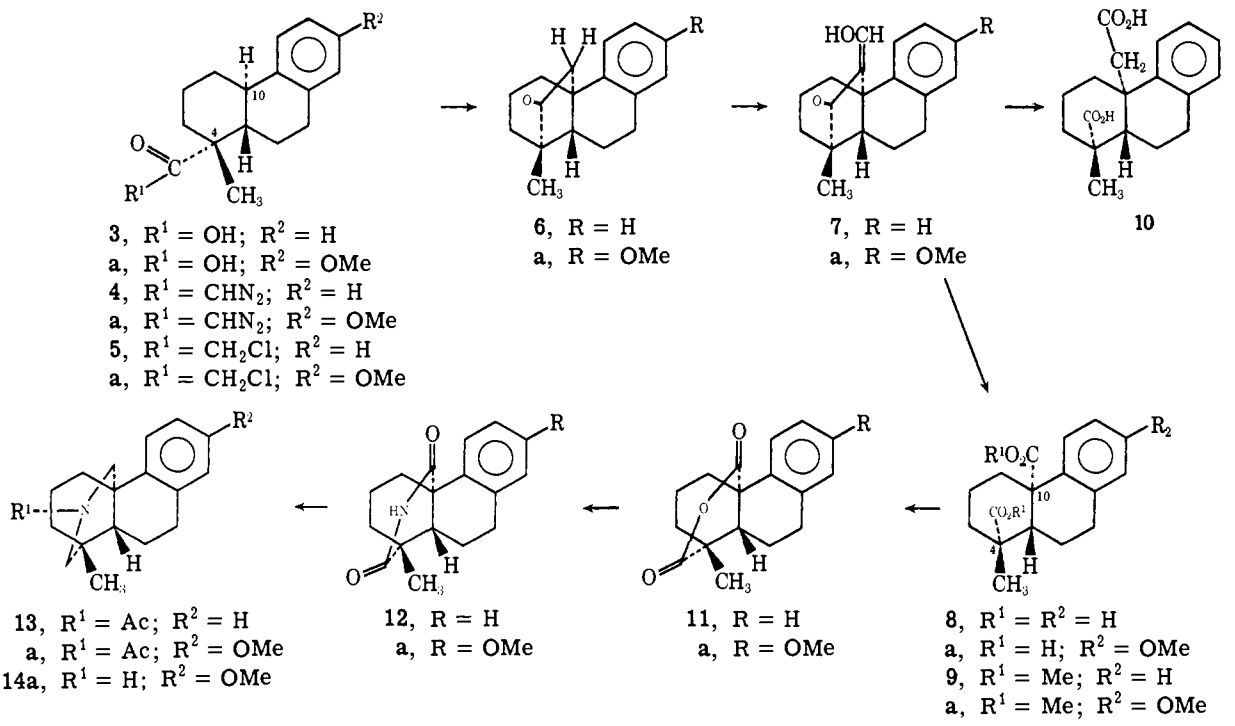
(5) See for examples: (a) J. W. ApSimon and O. E. Edwards, *Can. J. Chem.*, 40, 896 (1962); (b) W. L. Meyer and A. S. Levinson, *J. Org. Chem.*, 28, 2859 (1963); (c) I. Iwai and A. Ogiso, *Chem. Ind. (London)*, 1084 (1963); (d) D. H. R. Barton and J. R. Hanson, *Chem. Commun.*, 117 (1965); (e) A. Tahara and K. Hirao, *Tetrahedron Lett.*, 1453 (1966); (f) T. Matsumoto, M. Yanagiya, E. Kawakami, T. Okuno, M. Kakizawa, S. Yasuda, Y. Gama, J. Omi, and M. Matsunaga, *ibid.*, 1127 (1968); (g) P. Grafen, H. J. Kabbe, O. Roos, G. D. Diana, T. Li, and R. B. Turner, *J. Amer. Chem. Soc.*, 90, 6131 (1968).

(6) (a) U. R. Ghatak, N. R. Chatterjee, A. K. Banerjee, J. Chakravarty, and R. E. Moore, *J. Org. Chem.*, 34, 3739 (1969); (b) U. R. Ghatak and N. R. Chatterjee, *Indian J. Chem.*, 9, 804 (1971).

(7) See for other examples: (a) E. Wenkert, B. L. Mylari, and L. L. Davis, *J. Amer. Chem. Soc.*, 90, 3870 (1968); (b) J. K. Chakrabarti, S. S. Szinai, and A. Todd, *J. Chem. Soc. C*, 1303 (1970); (c) R. C. Cambie and R. A. Franich, *Aust. J. Chem.*, 24, 117 (1971).

(8) L. F. Johnson, J. Chakravarty, R. Dasgupta, and U. R. Ghatak, *Tetrahedron Lett.*, 1703 (1971).

(9) The synthetic compounds described are all racemates. Correct analytical figures have been obtained for all compounds for which physical and spectral data are given.



3, R^1 = OH; R^2 = H
a, R^1 = OH; R^2 = OMe
4, R^1 = CHN_2; R^2 = H
a, R^1 = CHN_2; R^2 = OMe
5, R^1 = CH_2Cl; R^2 = H
a, R^1 = CH_2Cl; R^2 = OMe

6, R = H
a, R = OMe

7, R = H
a, R = OMe

10

13, R^1 = Ac; R^2 = H
a, R^1 = Ac; R^2 = OMe
14a, R^1 = H; R^2 = OMe

12, R = H
a, R = OMe

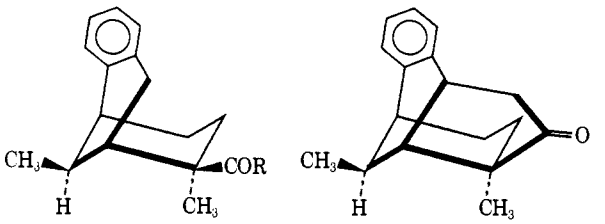
11, R = H
a, R = OMe

8, R^1 = R^2 = H
a, R^1 = H; R^2 = OMe
9, R^1 = Me; R^2 = H
a, R^1 = Me; R^2 = OMe

cyclohexane–tetrahydrofuran produced the known[5f,10] tetracyclic ketone **6**, mp 117–118° [ν_{max}^{Nujol} 1740 cm^{-1}; λ_{max}^{EtOH} 266 (log ϵ 2.65) and 274 nm (log ϵ 2.64); 220-MHz pmr[11] ($CDCl_3$) δ 1.045 (3 H, s), 2.395 (AB system, J = 20 Hz; $\Delta\nu_{AB}$ = 31.13 Hz)], in 45–50% yield (based on **3**) as the isolable crystalline product[12] after chromatography. The corresponding methoxy analog **4a** under the same sequence produced the tetracyclic ketone **6a**, mp 130° [*m/e* 270; $\nu_{max}^{CHCl_3}$ 1735 cm^{-1}; λ_{max}^{EtOH} 276 nm (log ϵ 3.55); 220-MHz pmr[11] ($CDCl_3$) δ 1.045 (3 H, s), 2.38 (AB system, J = 20 Hz, AB = 31.13 Hz)], in 20–25% overall yield from **3a** as the only crystalline product[13] along with a considerable amount of uncharacterized semisolid materials. The tetracyclic ketones have been transformed to a number of useful intermediates through the following simple synthetic methodology.[14]

Condensation of the ketone **6** with ethyl formate in the presence of sodium hydride afforded the hydroxymethylene derivative **7**, mp 132°, in 92% yield, which on oxidation with alkaline hydrogen peroxide[15] produced the dicarboxylic acid **8**, mp 232° dec, in 93% yield, and dimethyl ester **9** (diazomethane method), mp 135° (see Scheme I). A similar sequence of reactions with the methoxy tetracyclic ketone **6a** through the corresponding hydroxymethylene derivative **7a**, mp 124–125°, yielded the dicarboxylic acid **8a**, mp 232° dec, and dimethyl ester **9a**, mp 114°, in good yields.

Scheme I



1a, R = OH
1b, R = CHN_2

2

Reaction of the hydroxymethylene ketone **7** with hydroxylamine hydrochloride in acetic acid followed by basic cleavage[16] of the resulting product afforded the C-10 homologous dicarboxylic acid **10**, mp 232–233° dec, in 30% yield. These exemplify the usefulness of the present method for the stereospecific introduction of C-4,C-10 *cis*-dicarboxylic acid functionalities in a *trans*-hydrophenanthrene moiety for further transformation of these intermediates to various complex diterpenoids.

The conversion[5e] of the dicarboxylic acid **8** to the tetracyclic acetylamine **13** was achieved through the formation of the anhydride **11**, mp 194° [$\nu_{max}^{CHCl_3}$ 1800 and 1760 cm^{-1}], with boiling acetyl chloride followed by heating with urea to the imide **12**, mp 248° [$\nu_{max}^{CHCl_3}$ 1720 and 1705 cm^{-1}], in over 95% yield in each step. Finally, lithium aluminium hydride reduction of the imide in diglyme followed by acetylation of the crude amine produced the known acetylamine **13**,[5f,10] mp and mmp 126–127°, in 76% yield. In a similar sequence, the corresponding methoxy analog **8a** was converted to known racemic tetracyclic acetylamine **13a**,[5e,17] mp and mmp 165–166°, without purification of the intermediates **11a** and **12a**. The tetracyclic base **14a** served as the key intermediate in the

(10) We thank Professor Matsumoto for his help in providing the comparative spectral and mixture melting point data.
(11) We thank Dr. L. F. Johnson for the 220-MHz pmr spectrum.
(12) The only other product isolated in variable yields from this reaction product is the α-chloro ketone **5**, mp 133°. The formation of this undesirable product during the conversion of the corresponding acid chloride from **3** to the diazomethyl ketone **4** can be partially or completely suppressed by using triethylamine in the reaction (*cf.* ref 7c).
(13) The corresponding α-chloro ketone **5a**, mp 151°, was also isolated in variable yields (*cf.* ref 12).
(14) See ref 4d, 5f, and 5g for other approaches toward similar transformations.
(15) J. W. Huffman and P. G. Arapakos, *J. Org. Chem.*, 30, 1604 (1965).
(16) W. S. Johnson and W. E. Shelberg, *J. Amer. Chem. Soc.*, 67, 1745 (1945).
(17) We are indebted to Dr. Tahara for providing the comparison ir, glc, and mixture melting point data with the authentic sample.

total syntheses of racemic atisine,[4a] veatchine,[4b] and gibberellin-A_{15}[4c] by Nagata and coworkers.

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A New Synthetic Method for Ketone Methylenation. Reductive Elimination of Phenylthiomethylcarbinyl Esters

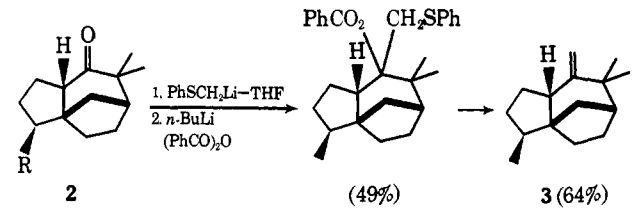
Sir:

Despite the impressive scope of the Wittig method for olefination of ketones and aldehydes with organophosphoranes,[1] this olefin synthesis does have certain limitations. Highly hindered ketones may be inert to methylenetriphenylphosphorane.[2] Proton transfer reactions may occur faster than carbonyl addition with the consequent risk of isomerization[3] and/or enolate condensation reactions.[1a]

We have found that acyl derivatives of the adducts between ketones and phenylthiomethyllithium (**1**),[4] one of the more stable functionalized methyl organometallics known,[5] are converted to olefins by reductive elimination.[6] This new two–three-step sequence constitutes a useful alternative method for the methylenation transformation which is operable with both sterically hindered and moderately acidic ketones and involves little risk of α epimerization or exchange *en route*.[7]

Reaction of phenylthiomethyllithium (**1**)[4] with a variety of cyclic ketones gives excellent yields of adducts which may be isolated by an aqueous quench,[4] or converted directly to the esters by treatment with an appropriate acylating reagent (see Table I).[9] While the consecutive addition–acylation reactions are usually both satisfactory and convenient, in some cases (*e.g.*, Δ^5-cholesten-3-one) it is advisable to isolate and purify the intermediate carbinol. The phenylthiomethyl carbinyl esters (acetate or benzoate) so obtained are smoothly transformed to the exocyclic methylene compounds by reduction with lithium in liquid ammonia.[10]

The methylenation of the thermodynamically unstable *cis*-1-decalone without detectable isomerization is noteworthy. Even the highly hindered tricyclic ketone (±)-norzizanone (**2**, R = CH_3)[11] undergoes



2 (49%) **3** (64%)

efficient addition with **1**, giving the alcohol adduct in 71% yield, in contrast to the very slow and inefficient Wittig reaction of norzizanoic acid (**2**, R = CO_2H).[12] (±)-Zizaene (**3**), free of epimeric or endocyclic isomers, was readily obtained by exposure of the benzoyl derivative (71%) to lithium in liquid ammonia.[11]

Use of **1**-d_2 provides a highly specific method for the preparation of deuterium-labeled olefins such as methylenecyclohexane-d_2 (>99% d_2). The Wittig reaction frequently leads to some loss of label and, in certain instances, positional scrambling.[13]

In order to evaluate the propensity of phenylthiomethyllithium (**1**) for proton removal, we selected as a model substrate the relatively acidic ketone, Δ^5-cholesten-3-one (**4**). Although a substantial amount of dienolate was evidently produced (42% ketone recovery) in the reaction between **1** and **4**, the two isomeric adducts (**5**α and **5**β, R = H) were formed in acceptable combined yield (55%). The two alcohols were separately benzoylated (**5**α, 65%; **5**β, 79%, R = PhCO) and reduced cleanly to the nonconjugated diene 3-methylene-Δ^5-cholestene (**6**, mp 108.5–110.5°, lit.[14] 109–110°). Direct reaction of **4** with methylenetriphenylphosphorane afforded impure **6** in <15% yield.

In addition to ketone methylenation this combination of reactions effects the two novel and useful transformations illustrated below. Methyl decanoate undergoes twofold addition with **1** at −25°, giving bisphenylthiomethylcarbinol (**9a**) (73%). Benzoylation and subsequent reduction with lithium–ammonia effects both vicinal elimination and allylic cleavage, yielding 2-methyl-1-undecene, to the exclusion of isomeric alkenes. This specific conversion of an ester to an isopropenyl group should find application in terpene synthesis.

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(2) J. E. McMurry, *J. Amer. Chem. Soc.*, **90**, 6821 (1968).

(3) C. H. Heathcock and R. Ratcliffe, *ibid.*, **93**, 1746 (1971); J. A. Marshall, M. T. Pike, and R. D. Carroll, *J. Org. Chem.*, **31**, 2933 (1966); M. D. Soffer and L. A. Burk, *Tetrahedron Lett.*, 211 (1970).

(4) E. J. Corey and D. Seebach, *J. Org. Chem.*, **31**, 4097 (1966).

(5) (a) J. Villiéras, *Organometal. Chem. Rev.*, 7, 81 (1971); (b) D. J. Peterson, *J. Amer. Chem. Soc.*, **93**, 4027 (1971), and pertinent references cited therein.

(6) The methodological concept of addition to an α-functionalized ketone followed by reductively directed elimination is the basis of the Cornforth olefin synthesis: J. W. Cornforth, R. H. Cornforth, and K. K. Mathew, *J. Chem. Soc.*, 112, 2539 (1959). This approach has found recent application in the synthesis of specific endocyclic olefins: T. M. Dawson, J. Dixon, P. S. Littlewood, B. Lythgoe, and A. K. Saksena, *J. Chem. Soc. C*, 2960 (1971).

(7) Although several useful alternative methods for olefination have been described,[5b,8] none have been shown capable of overcoming these difficulties.

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(9) All compounds gave nmr and ir spectral data in agreement with the indicated structures. Each final olefin, if previously unknown, was further characterized by a satisfactory combustion analysis. In all but two of the reaction sequences (those originating from the decalone and **2**), one or both of the intermediates gave satisfactory elemental analyses.

(10) The only unsuccessful case thus far encountered is dehydronorcamphor. The benzoyl derivative of the adduct with **1** gave <10% of the expected diene upon reduction with lithium–ammonia.[10a]

(10a) NOTE ADDED IN PROOF. The *p*-nitrobenzoyl ester is reduced smoothly (~75%) to 5-methylenenorbonene.

(11) R. M. Coates and R. L. Sowerby, *J. Amer. Chem. Soc.*, in press.

(12) F. Kido, H. Uda, and A. Yoshikoshi, *Chem. Commun.*, 1335 (1969).

(13) J. G. Atkinson, M. H. Fisher, D. Horley, A. T. Morse, R. S. Stuart, and E. Synnes, *Can. J. Chem.*, **43**, 1614 (1965); D. Seyferth, W. B. Hughes, and J. K. Heeren, *J. Amer. Chem. Soc.*, 87, 2847 (1965); O. E. Edwards and B. S. Mootoo, *Can. J. Chem.*, **47**, 1189 (1969); D. H. R. Barton, D. M. Harrison, G. P. Moss, and D. A. Widdowson, *J. Chem. Soc. C*, 775 (1970).

(14) G. Just and V. Di Tullio, *Can. J. Chem.*, **42**, 2153 (1964).