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

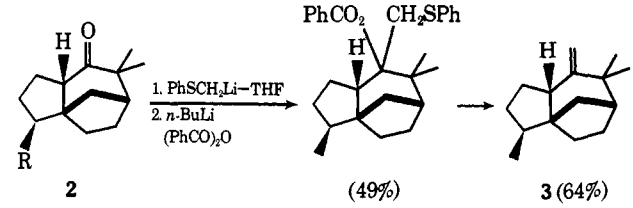
Sir:

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.

(1) (a) A. Maercker, *Org. React.*, **14**, 270 (1965); (b) S. Trippett, *Quart. Rev., Chem. Soc.*, **17**, 406 (1963); (c) H. J. Bestmann, *Bull. Soc. Chim. Fr.*, 1619 (1971); (d) A. W. Johnson, "Ylide Chemistry," Academic Press, New York, N. Y., 1966.

(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.

(8) (a) E. J. Corey and G. T. Kwiatkowski, *J. Amer. Chem. Soc.*, **90**, 6816 (1968); (b) E. J. Corey and G. T. Kwiatkowski, *ibid.*, **88**, 5653, 5654 (1966); (c) E. J. Corey and T. Durst, *ibid.*, **90**, 5548, 5553 (1968); (d) F. Bertini, P. Grasselli, G. Zubiani, and G. Cainelli, *Tetrahedron*, **26**, 1281 (1970); (e) G. Cainelli, A. U. Ronchi, F. Bertini, P. Grasselli, and G. Zubiani, *ibid.*, **27**, 6109 (1971); (f) T. H. Chan, E. Chang, and E. Vinokur, *Tetrahedron Lett.*, 1137 (1970); (g) D. J. Peterson, *J. Org. Chem.*, **33**, 780 (1968).

(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).

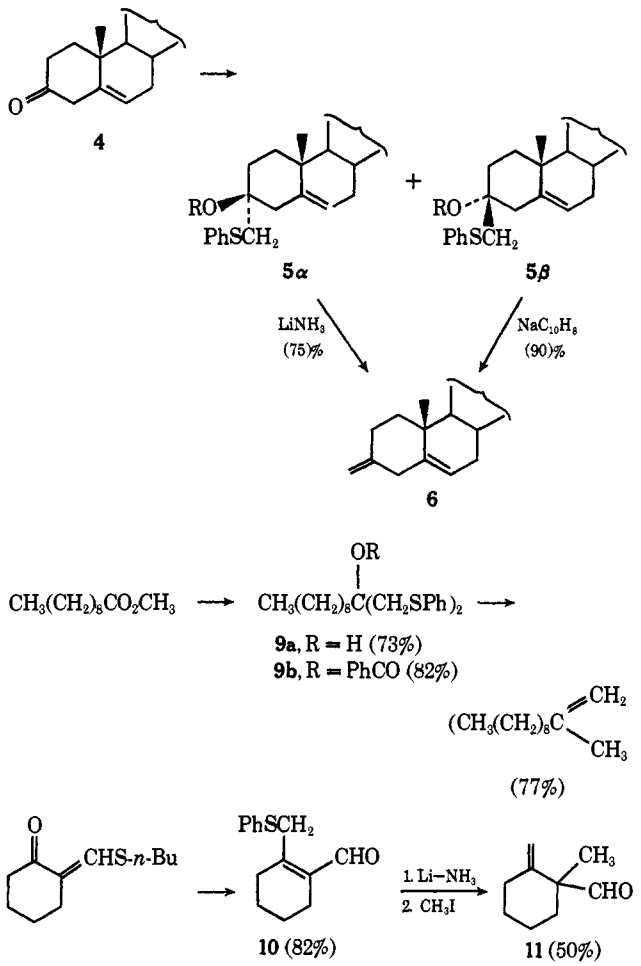
(13) J. G. Atkinson, M. H. Fisher, D. Horley, A. T. Morse, R. S. Stuart, and E. Synnes, *Can. J. Chem.*, **43**, 1614 (1965); D. Seyferth, W. B. Hughes, and J. K. Heeren, *J. Amer. Chem. Soc.*, **87**, 2847 (1965); O. E. Edwards and B. S. Mootoo, *Can. J. Chem.*, **47**, 1189 (1969); D. H. R. Barton,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

Table I. Ketone Methylenation *via* Phenylthiomethyllithium Addition, Acylation, and Reductive Elimination

Ketone	Acylating agent	Yield of ester,[a] %	Olefin (% yield)[b]
Cyclohexanone	$(CH_3CO)_2O$	82	Methylenecyclohexane (60)[c]
	$(C_6H_5CO)_2O$	77 (96)	
Cyclohexanone[d]	$(C_6H_5CO)_2O$	49	Methylenecyclohexane-d_2 (60)
2-Methylcyclohexanone	$(C_6H_5CO)_2O$	73	2-Methylmethylenecyclohexane (70)[c]
	C_6H_5COCl	72 (91)	
cis-1-Decalone[e]	$(C_6H_5CO_2)O$	73[e]	1-Methylenedecalin (50)[e]
	$(C_6H_5CO)_2O$	73 (81)[e]	
(±)-Norzizanone (**2**)	C_6H_5COCl	49 (71)	(±)-Zizaene (**3**, 64)
Δ^5-Cholesten-3-one (**4**)	$(C_6H_5CO)_2O$	18 α (27)	3-Methylene-Δ^5-cholestene (**6**, 75, 90[f])
		22 β (28)	3-Methylene-Δ^5-cholestene (**6**, 76)

[a] From ketone. The yield of the alcohol, if isolated, follows in parentheses. Conversion to the ester was achieved by lithiation (1 equiv of n-C_4H_9Li/THF), then acylation. [b] Lithium–ammonia reduction and isolated yield from ester unless indicated otherwise. [c] Yield by glc analysis. [d] Reaction with **1**-d_2. [e] Contains ~15% of trans-fused isomer. [f] Reduction with sodium–naphthalene in tetrahydrofuran.



Reaction of α-n-butylthiomethylenecyclohexanone[15] with **1** followed by dehydration of the rather unstable adduct with 10% hydrochloric acid and mercuric chloride in ethanol affords phenylthiomethylene aldehyde **10**. When **10** was subjected to reduction and methylation, the exocyclic β,γ-unsaturated aldehyde **11** was obtained.[16]

A typical procedure for ketone methylenation is as follows: *cis*-1-decalone (1.00 g, 6.57 mmol)[17] in 4 ml of tetrahydrofuran (THF) was added to a solution of **1** (7.3 mmol)[4] in THF–hexane (metallation of thioanisole with n-butyllithium–Dabco[4]) at 0°. After 3 hr at room temperature, the solution was recooled to 0° and benzoic anhydride (3.39 g, 15.0 mmol) in 5 ml of THF was added. After an additional 1.5 hr at room temperature, the mixture was diluted with pentane, filtered, and evaporated. Purification by silica gel chromatography afforded the benzoate (2.00 g, 78%)[17] as a pale yellow oil.

The benzoate (3.23 g, 8.50 mmol) in ether (60 ml) was added to a stirred, refluxing solution of lithium (0.35 g, 51.0 mmol) in liquid ammonia (165 ml) over a 30-min period. After another 30 min, pentane (60 ml) and then solid ammonium chloride (in small portions) were added prior to slow evaporation of the ammonia and addition of water. The pentane layer was combined with a second pentane extraction, washed with 1 N sodium hydroxide and water, dried ($MgSO_4$), and evaporated. Purification by chromatography on silica gel gave 0.65 g (~50%) of *cis*-1-methylenedecalin (>95% pure by glc analysis).[17]

Acknowledgment. We are grateful to the National Institutes of Health, the National Science Foundation, and Eli Lily and Co. for financial assistance.

(15) R. E. Ireland and J. A. Marshall, *J. Org. Chem.*, **27**, 1615 (1962); R. M. Coates and R. L. Sowerby, *J. Amer. Chem. Soc.*, **93**, 1027 (1971).

(16) In addition, 2-methyl-1-cyclohexenecarboxaldehyde was formed in ~20% yield.

(17) Containing ~15% of the trans fused isomer.

(18) University of Illinois Fellow, 1970–1971; Johnson and Johnson Fellow, 1971–1972.

(19) A. P. Sloan Foundation Fellow, 1971–1973.

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Syntheses of Actinomycin and Analogs. VIII. A Synthesis of Actinomycin D Lactam[1,2]

Sir:

Actinomycin D lactam (Chart I) has been synthesized in efforts to obtain analogs of the natural, clinically used antitumor agent which might possess improved therapeutic properties.[3,4] In this peptide analog both threonine residues of actinomycin D[5]

(1) Part VII: J. Meienhofer, R. Cotton, and E. Atherton, *J. Org. Chem.*, **36**, 3746 (1971). Supported, in part, by Public Health Service Research Grants C-6516 from the National Cancer Institute and FR-05526 from the Division of Research Facilities and Resources, National Institutes of Health.

(2) Abbreviations follow the rules of the IUPAC-IUB Commission on Biochemical Nomenclature in *Biochemistry*, **5**, 1445, 2485 (1966); **6**, 362 (1967); *J. Biol. Chem.*, **241**, 2491 (1966).

(3) S. Farber, *J. Amer. Med. Ass.*, **198**, 826 (1966).

(4) J. Meienhofer, *J. Amer. Chem. Soc.*, **92**, 3771 (1970).