25 g of neopentane was heated at 165° for 12 hr in a 240-ml bomb. The bomb was cooled and vented, and the contents were distilled to give 5.7 g of a colorless liquid, bp 95–100°, and 0.75 g of a black residue. Analysis of the residue indicated that it contained 5.25% N and 9.42% F. Gas chromatographic analysis on a silicone column of the distillate indicated two main components in the ratio 56:44. These components were separated on a preparative glpc column (fluorosilicone column). The principal component, having the longer retention time, was 1,1,1-trifluoro-2-(trifluoromethyl)-4,4-dimethylpentane (**15**): bp 101–102°; $n^{25}D$ 1.3301; ^{19}F nmr (neat) δ 6.83 (d, J = 8.4 Hz); H^1 nmr (neat) τ 9.05 (s, 3 CH_3), 8.29 (d, J = 4.5 Hz, C–CH_2–C), 7.18 (m, $C(CF_3)_2H$).

Anal. Calcd for $C_8H_{12}F_6$: C, 43.24; H, 5.45; F, 51.31. Found: C, 43.41; H, 5.49; F, 51.01.

The other component, with the shorter retention time, was 2,2-dimethyl-N-[2,2,2-trifluoro-1-(trifluoromethyl)ethylidene]-1-propylamine (**16**): bp 96–97°; $n^{25}D$ 1.3303; ^{19}F nmr (neat) δ 64.7 (quartet, J = 7.4 Hz to t, J = 2.7 Hz, 3 F) and 71.0 (quartet, J = 7.4 Hz to t, J = 2.0 Hz, 3 F); H^1 nmr (neat) τ 9.00 (s, 3 CH_3) and 6.45 (m, C–CH_2–N).

Anal. Calcd for $C_8H_{11}F_6N$: C, 40.86; F, 48.46; N, 5.96; H, 4.72. Found: C, 40.99; F, 48.58; N, 6.01; H, 4.69.

Reaction of Bis(trifluoromethyl)diazirine with Butane. A mixture of 15 g (0.084 mol) of bis(trifluoromethyl)diazirine and 40 g of *n*-butane was heated at 165° for 12 hr in a 400-ml stainless-steel bomb. The bomb was cooled and vented, and the contents were distilled to give 11.08 g of colorless liquid, bp 81–92°. Gas chromatographic analysis and ^{19}F nmr indicated four principal products present in the ratio 32:27:34:6 (by ^{19}F nmr integration). Preparative glpc (fluorosilicone column) gave the following compounds in order of retention time.

1-Methyl-N-[2,2,2-trifluoro-1-(trifluoromethyl)ethylidene]propylamine (**17**) was the original 32% component: bp 82–83°; ^{19}F nmr (neat) 63.4 ppm (quartet, J_{FF} = 7.7 Hz to d, J_{FH} = 2 Hz, 3 F) and 71.0 ppm (quartet, J = 7.7 Hz, 3 F).

Anal. Calcd for $C_7H_9F_6N$: C, 38.01; H, 4.10; F, 51.55; N, 6.34. Found: C, 38.31; H, 4.30; F, 51.72; N, 6.43.

1,1,1-Trifluoro-2-(trifluoromethyl)-3-methylpentane (**19**) was the original 27% component: bp 88–89°; ^{19}F nmr (neat), two pentets (probably overlapping quartets with J_{FF} and J_{FH} = *ca.* 8.5 Hz) centered at 62.1 ppm.

Anal. Calcd for $C_7H_{10}F_6$: C, 40.39; H, 4.84; F, 54.77. Found: C, 40.51; H, 4.92; F, 55.00.

1,1,1-Trifluoro-2-(trifluoromethyl)hexane (**20**) was the original 34% component: bp 88–89°; ^{19}F nmr (neat) 67.9 ppm (d, J = 8.1 Hz).

Anal. Calcd for $C_7H_{10}F_6$: C, 40.39; H, 4.84; F, 54.77. Found: C, 40.47; H, 4.90; F, 54.92.

N-[2,2,2-Trifluoro-1-(trifluoromethyl)ethylidene]butylamine (**18**) was the original 6% component: ^{19}F nmr (neat) 64.6 ppm (quartet, J_{FF} = 7.5 Hz to t, J_{FH} = 2.3 Hz, 3 F) and 71.1 ppm (quartet, J_{FF} = 7.5 Hz to t, H_{FH} = 1.6 Hz, 3 F).

Anal. Calcd for $C_7H_9F_6N$: C, 38.01; H, 4.10; F, 51.55; N, 6.34. Found: C, 38.32; H, 4.40; F, 51.60; N, 6.44.

Reaction of Hexafluoroacetone Azine (14) with Cyclohexane. A mixture of 25 ml of cyclohexane and 10.0 g of hexafluoroacetone azine was heated at 165° for 12 hr in a 145-ml bomb. The bomb was cooled and vented. Gas chromatographic analysis indicated only one major peak in addition to cyclohexane. Distillation gave 5.64 g (40%) of 2,2,2-trifluoro-1-(trifluoromethyl)ethylcyclohexane (**2**), bp 57–58° (25 mm), which was identified by comparison of its ir and nmr spectra with those of an authentic sample.

N-Cyclohexyl-1,1,1,3,3,3-hexafluoro-2,2-propanediamine (10). Method 1. Hexafluoroacetone imine, 25 ml, was distilled into 19.8 g (0.182 mol) of stirred cyclohexylamine over 45 min. Distillation at reduced pressure gave 35.1 g (70%) of the diamine **10** as a colorless liquid: bp 54–55° (4.4 mm); $n^{25}D$ 1.3903; ^{19}F nmr (neat) δ 80.2 (s).

Anal. Calcd for $C_9H_{14}F_6N_2$: C, 40.91; H, 5.34; F, 43.15; N, 10.61. Found: C, 40.97; H, 5.16; F, 43.35; N, 10.53.

Method 2. A mixture of 5 g of ammonia and 25 g of a 50:50 mixture of compounds 9 and **2** (prepared from cyclohexane and **8**) was heated at 100° in 8 hr in a 145-ml bomb. Distillation gave 6.77 g of **2**, bp 135°, and 6.70 g of the diamine **10**, bp 62–63° (3.8 mm). Both products were identified by comparison of their ir spectra with those of authentic samples.

Reaction of Bis(trifluoromethyl)diazirine with Benzene. A mixture of 50 ml of benzene and 10 g of bis(trifluoromethyl)diazirine was heated at 165° for 12 hr in a 240-ml stainless-steel bomb. The bomb was cooled and vented, and the contents were distilled to give 11.21 g (85%) of colorless liquid, bp 132–141°. Gas chromatographic analysis indicated the product was composed of 85% 7,7-bis(trifluoromethyl)-1,3,5-cycloheptatriene[4] and 15% [2,2,2-trifluoro-1-(trifluoromethyl)ethyl]benzene.[4]

A New Synthesis of Olefins from Carbonyl Compounds and Phoshonic Acid Bis Amides

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Contribution from the Department of Chemistry, Harvard University, Cambridge, Massachusetts 02138. *Received July 5, 1968*

Abstract: The reaction of α-lithio phosphonamide derivatives with aldehydes and ketones affords β-hydroxy phosphonamides by carbonyl addition in excellent yields. Thermal decomposition of these adducts in benzene or toluene solution at reflux leads to olefins by elimination of the elements of the corresponding phosphoric acid amide. β-Hydroxy phosphonamides can also be synthesized by reduction of β-keto phosphonamides, which in turn are available by the reaction of α-lithio phosphonamides with carboxylic esters. Methods for the stereoselective synthesis of a number of *cis* and *trans* olefins are described. The phosphonamide route to olefins is complementary to the Wittig and Horner–Emmons–Wadsworth methods, having certain general advantages which are discussed herein.

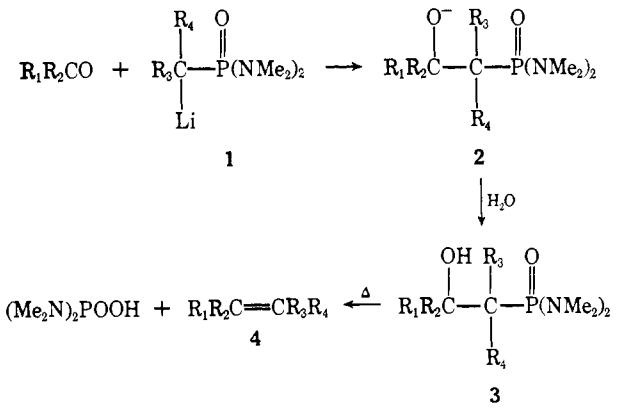
The discovery that β-hydroxy sulfinamides undergo thermal decomposition to olefins, amines, and sulfur dioxide (eq 1) suggested that the analogous trans-

$$R_2C(OH)CH_2SONHR' \xrightarrow{\Delta} R_2C{=}CH_2 + SO_2 + R'NH_2 \quad (1)$$

formation of β-hydroxy phosphonamides **3** to olefins and phosphoric acid bis amides might also occur.[1] As reported in a preliminary communication,[2] β-hydroxy phosphonamides **3** in fact do decompose readily in refluxing benzene to form olefins. This reaction, in conjunction with the carbonyl addition reaction illustrated

(1) (a) E. J. Corey and T. Durst, *J. Am. Chem. Soc.*, **88**, 5656 (1966); (b) E. J. Corey and T. Durst, *ibid.*, **90**, 5548 (1968).

(2) (a) E. J. Corey and G. T. Kwiatkowski, *ibid.*, **88**, 5652, 5653 (1966); (b) E. J. Corey, *Pure Appl. Chem.*, **14**, 19 (1967).

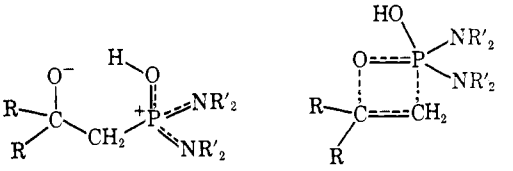


in the above sequence, constitutes an excellent and generally applicable method for the synthesis of olefins. Reported herein are the results from the application of alkylphosphonic acid bis(dimethylamides) to olefin synthesis; subsequent papers will deal with the extension of the reaction to other phosphonamides including those possessing functional groups. The bis(dimethylamides) have been used in the present study almost exclusively because of their availability and the ease of handling the parent compounds and their β-hydroxy derivatives.

The required carbanionic reagents of type **1** are generated conveniently and cleanly by reaction of an appropriate alkylphosphonic acid bis(dimethylamide) with 1 equiv of *n*-butyllithium. The effectiveness of this process is demonstrated by the conversion of aldehydes and ketones to β-hydroxy phosphonamides **3** in almost quantitative yields (see Tables I and II). Alkylation of the lithio derivatives **1** with suitable alkyl bromides and iodides is also a very efficient reaction. Thus, reaction of α-lithiomethylphosphonic acid bis(dimethylamide) (**1**, $R_3 = R_4 = H$) with methyl iodide, followed by the sequential addition of *n*-butyllithium and benzophenone afforded the adduct **3** ($R_1 = R_2 = C_6H_5$; $R_3 = CH_3$; $R_4 = H$) in 96% yield. The analogous sequence using *n*-butyl bromide or *n*-heptyl iodide afforded adducts **3** ($R_1 = R_2 = C_6H_5$; $R_3 = n\text{-}C_4H_9$; $R_4 = H$) and **3** ($R_1 = t\text{-}C_4H_9$; $R_2 = H$; $R_3 = n\text{-}C_7H_{15}$; $R_4 = H$) in 96 and 95% yields, respectively, starting from benzophenone and pivalaldehyde.

As anticipated, the anionic adducts **2**, in contrast to the β-alkoxy phosphonothionates and the β-alkoxy phosphonium betaines (intermediates in the Wittig process) are not prone to olefin-forming elimination.[3] However, the hydroxy adducts **3** readily undergo elimination to yield olefins at reflux in benzene or toluene solution. There is some variation in the rate of olefin formation dependent upon the structure of **3**. In general, adducts derived from ketones decompose faster than those derived from aldehydes, and substitution on the α-carbon also increases the rate of decomposition.[4]

The formation of olefins by thermal decomposition of β-hydroxy phosphonic acid bis amides probably involves a zwitterionic intermediate of type **5** which undergoes *cis* cycloelimination. A similar *cis*-elimination process has already been demonstrated in the case of the



analogous decomposition of β-hydroxy sulfinamides to olefins.[5] The marked dependence of the rate of elimination on the degree of substitution on the α- and β-carbon atoms is consistent with a transition state in which CO and CP bond breaking are well advanced, *e.g.*, **6**.

The scope of the phosphonamide route to olefins appears to be broad, since mono-, di-, tri-, and tetrasubstituted ethylenic derivatives can all be synthesized by this method (see Tables I and II). The ease with which tetrasubstituted olefins can be prepared in high yield is of special interest. For example, α-lithioisopropylphosphonic acid bis(dimethylamide) reacts with benzophenone to produce an adduct, **3** ($R_1 = R_2 = C_6H_5$; $R_3 = R_4 = CH_3$), in 94% yield, which upon heating gives 1,1-diphenyl-2-methylpropene in 92% yield. Phosphonic acid bis(dimethylamides) are generally available from the reaction of phosphonyl dichlorides with dimethylamine.[6] A large number of phosphonyl dichlorides can be prepared by alkylation of phosphorus trichloride using an alkyl chloride and aluminum trichloride followed by controlled hydrolysis.[7] In addition, a wide

$$RCl + PCl_3 + AlCl_3 \longrightarrow (RPCl_3)^+(AlCl_4)^- \xrightarrow{H_2O} RP(O)Cl_2$$
$$RP(O)Cl_2 + Me_2NH \longrightarrow RP(O)(NMe_2)_2$$

variety of more complex phosphonic acid bis amides can be produced by the alkylation of the α-lithio derivatives of simpler phosphonic acid amides.

Table I. Conversion $R_1R_2C{=}O \longrightarrow R_1R_2C{=}CH_2$ *via* Methylphosphonic Acid Bis(dimethylamide) Adducts

Carbonyl compd	Yield of adduct, %	Yield of olefin, %[a]
Benzophenone	95	93
4-*t*-Butylcyclohexanone	98	65[b]
2-Cyclohexenone	96	78[c,d]
Benzaldehyde	95	53[c]
Δ^3-Cyclohexenecarboxaldehyde	95	67[c]
Dodecanal	89	70[c]

[a] Yields given refer to reaction in benzene at reflux for 12 hr. [b] Yield of isolated product. [c] Yield as determined by vpc or nmr analysis. [d] Elimination carried out without silica gel and in the presence of triethylamine to prevent isomerization of the olefinic product.

Table II. Conversion $R_1R_2C{=}O \longrightarrow R_1R_2C{=}CHCH_3$ *via* Ethylphosphonic Acid Bis(dimethylamide) Adducts

Carbonyl compd	Yield of adduct, %	Yield of olefin, %
Benzophenone	97	90
4-*t*-Butylcyclohexanone	92	80
Benzaldehyde	98	90[a,b]
Δ^3-Cyclohexenecarboxaldehyde	96	79[a]
Acetophenone	74	90

[a] For stereochemistry see E. J. Corey and G. T. Kwiatkowski, *J. Am. Chem. Soc.*, **88**, 5653 (1966). [b] Yield for reaction in toluene at reflux for 12 hr; all other yields for reaction in benzene at reflux for 12 hr.

(3) β-Alkoxy sulfinamides are also not particularly susceptible to olefin-forming eliminations; see ref 1.

(4) The rate of reaction may also be increased by a factor of approximately 2 by employing silica gel (Woelm) as a catalyst.

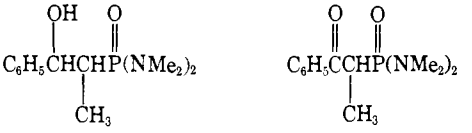
(5) E. J. Corey and T. Durst, *J. Am. Chem. Soc.*, **90**, 5553 (1968).

(6) G. M. Kosolapoff and L. B. Payne, *J. Org. Chem.*, **21**, 413 (1956).

(7) A. M. Kinnear and E. A. Perren, *J. Chem. Soc.*, 3437 (1952).

The efficiency of the phosphonamide route to olefins and the isolability of the intermediate β-hydroxy phosphonamides suggested that directed synthesis of *cis* and *trans* olefins might be achievable by this method. Since one serious limitation of the Wittig reaction is the difficulty of controlling olefinic geometry,[8] such a result would be of considerable utility. The unique stability of the intermediate β-hydroxy phosphonamides **3** simplifies the task of selecting experimental conditions which favor the desired stereochemical pathway and allows the purification of the proper diastereomeric adduct **3** by recrystallization.

In practice, the separation of diastereomeric β-hydroxy phosphonamides by recrystallization has proven to be a relatively simple procedure due to the ease with which these substances crystallize. Thus, even if adduct formation is nonstereospecific, the products can be purified by recrystallization prior to the olefin-forming step. The procedure has been used to synthesize pure *cis*-1-phenylpropene and *cis*-2-phenyl-2-butene. The preparation of *cis*-1-phenylpropene is illustrative. Addition of benzaldehyde to α-lithioethylphosphonic acid bis(dimethylamide) in tetrahydrofuran gave the β-hydroxy phosphonamide **8** in 98% yield as a mixture of diastereomers **8a** and **8b** in a ratio of 2.5:1.[9] The predominant diastereomer was purified by recrystallization;[10] thermolysis in benzene at reflux afforded pure *cis*-1-phenylpropene.[11]



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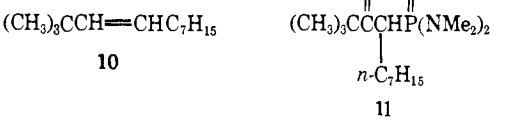
An alternative route *via* β-hydroxy phosphonamides was developed for the synthesis of *trans* olefins. The method is based on the stereoselective reduction of the carbonyl group of β-keto phosphonamides. By proper choice of reagents it has been possible to obtain, with a high degree of selectivity, the diastereomeric precursor to the *trans* olefin. Thus, reduction of β-keto phosphonamide **9**, prepared in 79% yield by the addition of methyl benzoate to α-lithioethylphosphonic acid bis(dimethylamide), with sodium borohydride in methanol afforded diastereomer **8b** in 80% yield and with 98% stereospecificity. Decomposition of **8b** in refluxing toluene after recrystallization yielded pure *trans*-1-phenylpropene.[11]

The utility of the keto phosphonamide route to olefins is further illustrated by its application to the synthesis of *trans*-1-*t*-butyl-1-nonene (**10**). Generally, the synthesis of 1-*t*-butyl-1-alkenes by reaction of the appropriate Wittig reagent with pivalaldehyde affords predominantly the *cis* isomer. For example, treatment of the ylide *n*-octylidenetriphenyl phosphorane [$(C_6H_5)_3PCHC_7H_{15}$] with pivalaldehyde in dimethyl sulfoxide produces a mixture of *cis*- and *trans*-1-*t*-butyl-1-nonenes (**10**) containing 98.5% of the *cis* isomer.[12] In contrast, reduction of the keto phosphonamide **11**, obtained in



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97% yield by the reaction of methyl pivalate with α-lithio-*n*-octylphosphonic acid bis(dimethylamide) (2 equiv), with lithium aluminum hydride–aluminum chloride followed by *t*-butoxide equilibration[13,14] gave an approximately 93:7 mixture of two diastereomeric β-hydroxy phosphonamides which could be decomposed selectively to give pure *trans*-1-*t*-butyl-1-nonene in 71% yield. In general, the rate of decomposition of a diastereomeric β-hydroxy phosphonamide leading to a *trans* olefin is faster than that of the corresponding diastereomer leading to the *cis* analog. As a result, it was possible to prepare pure *trans*-1-*t*-butyl-1-nonene from the mixture containing 93% of the precursor of this *trans* olefin by limiting the decomposition time.

A number of features of the β-keto phosphonamide route to olefins are worthy of note. The required β-keto phosphonamides are easily prepared by either direct addition of an α-lithio phosphonamide to an ester or oxidation of the β-hydroxy analog. In addition to the method described above, the β-keto adduct **9** was also prepared in 91% yield by oxidation of **8** with activated manganese dioxide. Secondly, a wide range of reagents are available for the reduction of β-keto phosphonamides. The following have all been used successfully: sodium and lithium borohydride, lithium alkoxyaluminum hydride, hydrogen–Raney nickel, aluminum amalgam, diborane, and disiamylborane. Thirdly, even when the available β-hydroxy phosphonamide is a mixture containing the unwanted diastereomer, the *trans* olefin can be obtained selectively simply by limiting the extent of conversion to olefin.

The above findings suggest that the phosphonamide route to olefins in its various forms will prove to be a general and useful synthetic method. In certain respects the phosphonamide method is complementary to the Wittig olefin synthesis, having distinct advantages in certain situations to which the latter is not particularly well suited. These advantages may arise from the following possibilities: (1) the elaboration of carbon structure of the phosphonamide system by alkylation (phosphonium ylides generally do not undergo smooth alkylation), (2) the direction or control of stereochemistry in the formation of the β-hydroxy phosphonamide intermediate by carbonyl addition, (3) the purification of the intermediate β-hydroxy phosphonamide prior to olefin generation, (4) the alternative route to β-hydroxy phosphonamides *via* β-keto phosphonamides, and (5) the conversion of an undesired stereoisomeric β-hydroxy

(8) (a) Recent work by a number of investigators has demonstrated that the stereoselectivity of the Wittig reaction can be substantially altered by varying the reaction conditions; see A. W. Johnson, "Ylid Chemistry," Academic Press, New York, N. Y., 1966, p 184, and M. M. Shemyakin in "Organo-phosphorus Compounds," Butterworth and Co. (Publishers) Ltd., London, 1964, p 271; (b) see also M. Schlosser, *et al.*, *Angew. Chem. Intern. Ed. Engl.*, **5**, 126, 667 (1966).

(9) The relative amounts of the two diastereomers depend on solvent. The ratio of **8a** and **8b** was 3.5:1 in 4:1 toluene–tetrahydrofuran, for example.

(10) The nmr spectrum of the diastereomeric mixture can be used to determine the effectiveness of the recrystallization process, since the spectra of the individual diastereomers are sufficiently different to provide accurate measures of purity.

(11) R. Y. Mixer, R. F. Heck, S. Winstein, and W. G. Young, *J. Am. Chem. Soc.*, **75**, 4094 (1953).

(12) E. J. Corey and E. Hamanaka, *ibid.*, **89**, 2758 (1967).

(13) Method of E. L. Eliel and M. N. Rerick, *ibid.*, **82**, 1367 (1960).

(14) The ketone **9** was not reduced by sodium borohydride under a variety of conditions.

phosphonamide produced by carbonyl addition to the desired diastereomer *via* the corresponding β-keto phosphonamide. The ready availability and potential low cost of the phosphonamide reagents is another factor which would seem to favor their application. The Horner–Emmons–Wadsworth method[15] for the synthesis of α,β-unsaturated carbonyl compounds is complementary to both the Wittig and phosphonamide routes to olefins.

Further work is in progress on the stereochemical course of the phosphonamide route to olefins and on the use of phosphonamide reagents bearing functional groups, the results of which will be reported in due course.

Experimental Section

General Method for the Preparation of Alkylphosphonic Acid Bis Amides as Illustrated by Methylphosphonic Acid Bis(dimethylamide). The procedure of Kinnear and Perren[7] was followed. A glass bomb was charged with 69.3 g (0.48 mol) of phosphorus trichloride, 80 g (0.60 mol) of aluminum chloride, and 31 g (0.61 mol) of methyl chloride. The solution was then stirred magnetically as the bomb was cooled in a water bath (to moderate the strongly exothermic reaction) at room temperature for 4 hr. The solidified reaction mixture was dissolved in 900 ml of methylene chloride, and 120 ml of water was added slowly with cooling. The resulting solid was removed by filtration, and the filtrate was evaporated under vacuum. Distillation afforded 33.5 g (53%) of methylphosphonic dichloride, bp 60° (11 mm), mp 34° (lit.[7] mp 33°).

The method of Kosolapoff[6] was adapted for the synthesis of methylphosphonic acid bis(dimethylamide). To a stirred solution of 18.0 g (0.40 mol) of dimethylamine in 250 ml of ethyl ether was added, while at 0° and under nitrogen, 10.0 g (0.0753 mol) of methylphosphonic dichloride. The resulting solution was stirred at 0° for 1 hr and at 25° for 3 hr. The precipitate of dimethylamine hydrochloride was removed by filtration and the filtrate evaporated under vacuum. Distillation of the residue afforded 10.0 g (89%) of methylphosphonic acid bis(dimethylamide), bp 74–75° (1.5 mm) (lit.[6] bp 138° (32 mm)). The nmr spectrum ($CDCl_3$) showed two doublets at 1.61 (area 3, J = 15) and 2.62 (area 12, J = 10) ppm.[16]

α-Lithiomethylphosphonic Acid Bis(dimethylamide). To a stirred solution of 1.0 g (6.67 mmol) of methylphosphonic acid bis(dimethylamide) in 15 ml of dry tetrahydrofuran (distilled from lithium aluminum hydride) was added, while under nitrogen and at −78°, 4.35 ml (6.95 mmol) of a 1.6 *M* solution of *n*-butyllithium in hexane. Complete metallation required approximately 15 min at −78°, at which point the reagent could be utilized in reactions or stored at Dry Ice temperatures. The reagent was shown to be stable at ambient temperature for short periods of time.

α-Lithioethylphosphonic Acid Bis(dimethylamide). A stirred solution containing 1.0 g (6.09 mmol) of ethylphosphonic acid bis(dimethylamide) in 15 ml of dry tetrahydrofuran (distilled from lithium aluminum hydride) was treated, while at −78° and under nitrogen, with 3.9 ml (6.25 mmol) of 1.6 *M n*-butyllithium in hexane. The mixture required stirring at −50° for 3 hr to effect complete metallation.

Reaction of α-Lithiomethylphosphonic Acid Bis(dimethylamide) with Benzophenone. A solution of α-lithiomethylphosphonic acid bis(dimethylamide) was prepared under nitrogen using 6.24 mmol of *n*-butyllithium in 20 ml of tetrahydrofuran. To this solution, with stirring at −78°, was added 1.091 g (6 mmol) of benzophenone in one portion. The reaction mixture was allowed to stir at −78° for 0.5 hr and then allowed to warm at room temperature for 0.5 hr, after which 10 ml of water was added, and the mixture was extracted with ether. The combined extracts were washed with water, dried over magnesium sulfate, and evaporated to yield a white solid. Recrystallization from pentane–ether afforded 1.89 g (95%) of the β-hydroxy phosphonamide adduct, mp 155–157°.

Anal. Calcd for $C_{18}H_{25}N_2O_2P$: C, 65.04; H, 7.58. Found: C, 65.91; H, 7.63.

Reaction of α-Lithiomethylphosphonic Acid Bis(dimethylamide) with Benzaldehyde. A solution of α-lithiomethylphosphonic acid bis(dimethylamide) was prepared at −78° from 6.95 mmol of *n*-butyllithium in 15 ml of tetrahydrofuran. To this solution with stirring and under nitrogen was added 0.709 g (6.67 mmol) of benzaldehyde. After stirring at −78° for 1.5 hr and between −70 and 25° for 0.5 hr, 5 ml of water was added, and the mixture was extracted with ether. The combined ether extracts were washed with water, dried, and evaporated under vacuum to give, after recrystallization, a white solid, 1.616 g (95%), mp 87–88°.

Anal. Calcd for $C_{12}H_{21}N_2O_2P$: C, 56.23; H, 8.26. Found: C, 56.42; H, 8.31.

The nmr spectrum ($CDCl_3$) showed a doublet at 2.08 (area 1, J = 13), a doublet of doublets at 2.2 (area 1, J = 13, 2) (nonequivalent methylene protons), doublets at 2.5 and 2.62 (area 12, J = 9), a multiplet at 4.95 (area 1), a broad doublet at 5.45 (area 1, OH), and a multiplet at 7.33 (area 5) ppm.

Reaction of α-Lithiomethylphosphonic Acid Bis(dimethylamide) with 4-*t*-Butylcyclohexanone. To a stirred solution of α-lithiomethylphosphonic acid bis(dimethylamide), prepared from 6.95 mmol of *n*-butyllithium in 15 ml of tetrahydrofuran was added 1.029 g (6.67 mmol) of 4-*t*-butylcyclohexanone. After stirring at −78° for 2 hr and at −70 to +25° for 1 hr, 10 ml of water was added and the mixture extracted with ether. The extracts were washed with water, dried, and evaporated under vacuum. Recrystallization of the residue from pentane–ether gave 1.99 g (98%) of a white solid, mp 86–88°.

Reaction of α-Lithioethylphosphonic Acid Bis(dimethylamide) with Benzaldehyde. A solution of α-lithioethylphosphonic acid bis(dimethylamide) was prepared at −50° and under nitrogen from 3.2 mmol of *n*-butyllithium in 15 ml of tetrahydrofuran. With stirring, 0.323 g (3.05 mmol) of benzaldehyde was added in one portion, after which the reaction mixture was allowed to stand at −50° for 0.5 hr and at −50 to +25° for 0.5 hr. Water was then added and the resulting mixture extracted with ether; the combined extracts were washed with water, dried over magnesium sulfate, and evaporated under vacuum to afford 0.775 g (94%) of an oil. The oily residue was dissolved in pentane–ether (1:1) and allowed to stand at −20° for 30 hr to obtain 0.382 g of a white solid, mp 78–80°. Recrystallization from pentane–ether (4:1) raised the melting point to 80.5–82°. The mother liquors contained the above compound and its diastereomer.

Anal. Calcd for $C_{13}H_{22}N_2O_2P$: C, 57.76; H, 8.58. Found: C, 57.26; H, 8.59.

The nmr spectrum of the major diastereomeric product, mp 80.5–82°, showed a doublet of doublets centered at 0.94 (J_{HH} = 7.5, J_{HP} = 17, area 3), a multiplet centered at 2.3 (area 1), a triplet (overlapping doublets) at 2.70 (area 12, J = 8), a broad singlet at 5.0 (area 1, OH), a broad doublet at 5.25 (area 1, J = 8), and a broad singlet at 7.3 (area 5) ppm. The nmr spectrum of the other diastereomer showed a doublet of doublets at 0.75 (J_{HH} = 7.5, J_{HP} = 17, area 3), a multiplet at 2.4 (area 1), doublets at 2.65 and 2.80 (J = 10, 8, area 12), a triplet at 4.68 (J = 9, area 1), a broad singlet at 6.40 (area 1, OH), and a broad singlet at 7.35 (area 5) ppm.

***In Situ* Preparation of Ethylphosphonic Acid Bis(dimethylamide). Generation of the Corresponding Anion and Reaction with Benzophenone.** A tetrahydrofuran solution (20 ml) containing 6.8 mmol of α-lithiomethylphosphonic acid bis(dimethylamide) was prepared under nitrogen. While at −78°, 0.965 g (6.8 mmol) of methyl iodide was added and the reaction mixture stirred at −78° for 0.2 hr and at −78 to +25° for 0.5 hr. The solution was cooled again at −78°, and 4.25 ml (6.8 mmol) of 1.6 *M n*-butyllithium was added (precipitate of lithium iodide). The reaction mixture was stirred at −50° for 3 hr, and 1.20 g (6.6 mmol) of benzophenone was then added. Stirring was continued for 0.5 hr, after which water was added, and the reaction mixture was extracted with ether. The combined extracts were washed with water, dried, and evaporated under vacuum to give a pale yellow solid, 2.19 g (96%), mp 156–158°, after recrystallization and identical with **3** (R_1 = R_2 = C_6H_5; R_3 = H; R_4 = CH_3), prepared as described above. The nmr spectrum of the crude product showed only a trace of the unmethylated benzophenone adduct and indicated >95% purity.

Reaction of α-Lithioethylphosphonic Acid Bis(dimethylamide) with Acetophenone. To a stirred solution containing 5.0 mmol of α-lithioethylphosphonic acid bis(dimethylamide) in 15 ml of tetrahydrofuran was added 0.600 g (5.0 mmol) of acetophenone, while at −70° and under nitrogen. After stirring at −70° for 2 hr and at −70 to +25° for 1 hr, 10 ml of water was added. The mixture was extracted with ether; the ether extracts were washed with water, dried, and evaporated under vacuum to afford an oil. The oil,

(15) (a) L. Horner, H. Hoffmann, W. Klink, H. Ertel, and V. G. Toscano, *Ber.*, **95**, 581 (1962); (b) W. S. Wadsworth and W. D. Emmons, *J. Am. Chem. Soc.*, **83**, 1733 (1961).

(16) Nuclear magnetic resonance data were obtained at 60 MHz; chemical shifts are expressed in parts per million downfield from internal tetramethylsilane and coupling constants (J) as hertz.

shown by infrared to contain acetophenone, was crystallized from pentane–ether (10:1) to give a 1.044-g (74%) mixture of two diastereomers, mp 99–111°.

Anal. Calcd for $C_{14}H_{25}N_2O_2P$: C, 57.14; H, 8.86. Found: C, 59.04; H, 8.93.

A second recrystallization of the above solid from ether–pentane (3:2) gave a mixture containing 95% of the diastereomeric precursor to *cis*-2-phenyl-2-butene.

The nmr spectrum ($CDCl_3$) of the diastereomer leading to *cis* olefin showed a doublet of doublets at 0.92 (J_{HH} = 7.5, J_{HP} = 17), a singlet at 1.60, doublets at 2.43 (J = 10) and 2.70 (J = 8), a broad singlet at 6.6, and multiplets centered at 7.4 ppm. The nmr spectrum ($CDCl_3$) of the diastereomer leading to the *trans* olefin showed a doublet of doublets at 0.90 (J_{HH} = 7.5, J_{HP} = 17), a singlet at 1.53, doublets at 2.38 (J = 10) and 2.69 (J = 8), a singlet at 5.95, and a multiplet at 7.3 ppm.

In Situ **Preparation of *n*-Octylphosphonic Acid Bis(dimethylamide). Generation of the Corresponding Anion and Reaction with Pivalaldehyde.** To a stirred solution of 3.0 mmol of α-lithiomethylphosphonic acid bis(dimethylamide) in 18 ml of tetrahydrofuran was added, while under nitrogen and at −78°, 0.678 g (3.0 mmol) of 1-iodoheptane. Stirring was continued at −70° for 15 hr and at −70 to +25° for 1 hr. The solution was cooled again to −70°, and 2.0 ml (3.2 mmol) of 1.6 *M n*-butyllithium was added. After 4 hr at −70°, 0.258 g (3.0 mmol) of pivalaldehyde was added, and the reaction mixture was stirred at −70° for 2 hr and at −70 to +25° for 15 min. Water was then added, and the mixture was extracted with ether; the combined ether extracts were washed with water, dried, and evaporated under vacuum to afford 0.954 g (95%) of an oil (mixture of diastereomers). The nmr spectrum ($CDCl_3$) showed multiplets centered at 0.95 (area 12), 1.3 (area 12), 2.0 (area 1), 3.6 (area 1), and 5.1 (area 1), and a doublet at 2.68 (J = 9, area 12) ppm.

Reaction of α-Lithioisopropylphosphonic Acid Bis(dimethylamide) with Benzophenone. To a stirred solution of 0.356 g (2 mmol) of isopropylphosphonic acid bis(dimethylamide) (prepared by addition of methyl iodide to α-lithioethylphosphonic acid bis(dimethylamide), bp 62–64° (0.02 mm)) in 10 ml of tetrahydrofuran was added, while at −50° and under nitrogen, 1.3 ml (2.08 mmol) of 1.6 *M n*-butyllithium. Stirring was continued for 5.5 hr at approximately −40°, after which 0.364 g (2.0 mmol) of benzophenone was added. This mixture was stirred at −40° for 0.5 hr and at −40 to +25° for 0.5 hr. Water was then added, and the reaction products were extracted with ether and the combined ether extracts washed with water, dried, and evaporated. A white solid was thereby obtained, 0.675 g (94%), mp 130–131°.

Anal. Calcd for $C_{20}H_{29}N_2O_2P$: C, 66.64; H, 8.11. Found: C, 66.63; H, 8.29.

Olefin Formation by Elimination of β-Hydroxyalkylphosphonic Acid Bis(dimethylamides). General Procedure. A stirred solution of the β-hydroxyalkylphosphonic acid bis(dimethylamide) in approximately 10 times the weight of benzene and 2–3 times the weight of silica gel (Woelm) was heated at reflux for 3–12 hr, the reaction being monitored by nmr spectroscopy. Generally, the times required for complete olefin formation were as follows: conjugated di-, tri-, and tetrasubstituted olefins 3–6 hr; tri- and tetrasubstituted olefins 4–8 hr; disubstituted olefins 7–10 hr; and monosubstituted olefins 10–12 hr. The reaction time can be shortened if refluxing toluene is used in place of benzene. After the requisite period of time, ethyl ether was added and the solution filtered. After washing the silica gel further with ether, the combined filtrates were washed with water, dried over magnesium sulfate, and concentrated. In most cases the washing step can be neglected, since the phosphoric acid bis(dimethylamide) remains on the silica gel. Distillation afforded pure olefin directly. Yields were determined by direct weighing or by vpc analysis using an internal standard. The olefinic products were examined by nmr and infrared spectroscopy in each case in order to verify their structures.

1,1-Diphenylethylene. A solution of 1.55 g of β-hydroxy phosphonamide **3** ($R_1 = R_2 = C_6H_5$; $R_3 = R_4 = H$) in 25 ml of benzene containing 3.2 g of silica gel was heated at reflux for 12 hr. Ether, 25 ml, was then added and the mixture filtered. Evaporation of the solvent and distillation of the residue in a bulb-to-bulb apparatus afforded 0.785 g (93%) of 1,1-diphenylethylene, spectroscopically identical with authentic material.

4-Methylene-*t*-butylcyclohexane. A solution containing 1.7 g of β-hydroxy phosphonamide **3** (R_1R_2C = 4-*t*-butylcyclohexyl; $R_3 = R_4 = H$) in 25 ml of benzene containing 6.7 g of silica gel was heated at reflux for 11 hr. Ether, 25 ml, was added and the mixture filtered. The solvent was removed under vacuum and the residue distilled in a bulb-to-bulb apparatus to give 0.55 g (65%) of 4-methylene-*t*-butylcyclohexane, spectroscopically identical with authentic material.

1,1-Diphenylpropene. A mixture containing 1.5 g of β-hydroxy phosphonamide **3** ($R_1 = R_2 = C_6H_5$; $R_3 = CH_3$; $R_4 = H$) and 5.0 g of silica gel in 15 ml of benzene was heated at reflux for 10 hr. The mixture was diluted with 25 ml of ether and filtered. The filtrate was evaporated under vacuum and the residue distilled in a bulb-to-bulb apparatus to afford 0.791 g (90%) of 1,1-diphenylpropene, mp 46–47°, spectroscopically identical with authentic material.

1,1-Dimethyl-2,2-diphenylethylene. A solution of 0.247 g of β-hydroxy phosphonamide **3** ($R_1 = R_2 = C_6H_5$; $R_3 = R_4 = CH_3$) in 8 ml of benzene containing 0.56 g of silica gel was heated at reflux for 10 hr. Ether was added and the mixture filtered. The filtrate was evaporated to 0.138 g (95%) of 1,1-dimethyl-2,2-diphenylethylene, spectroscopically identical with authentic material.

***cis*-1-Phenylpropene.** A 0.135-g sample of β-hydroxy phosphonamide **3** ($R_1 = C_6H_5$; $R_2 = R_3 = H$; $R_4 = CH_3$), mp 80.5–82°, was heated at reflux for 15 hr in 5 ml of benzene containing 0.40 g of silica gel. Vpc analysis (silicon oil column) indicated that only *cis*-1-phenylpropene was present. The reaction mixture was diluted with 15 ml of ether, filtered, and evaporated under vacuum. The infrared spectrum of the product was identical with that reported for *cis*-1-phenylpropene.[11]

***trans*- and *cis*-1-*t*-Butyl-1-nonenes.** A solution of 0.334 g of β-hydroxy phosphonamide **3** ($R_1 = (CH_3)_3C$; $R_2 = R_3 = H$; $R_4 = n\text{-}C_7H_{15}$) and 0.5 g of silica gel in 4 ml of toluene was heated at reflux for 13 hr. After cooling, 10 ml of ether was added, and the mixture was filtered. Vpc analysis of the filtrate showed that a 3.1:1.0 ratio of *trans*- and *cis*-1-*t*-butyl-1-nonenes[12] was obtained in 80% yield (decane as an internal standard). The nmr spectrum of the residue after evaporation of the solvent showed a singlet at 1.00 ppm for the *t*-butyl group in the *trans* olefin and a singlet at 1.11 ppm for the *t*-butyl group in the *cis* olefin.

2-Phenyl-2-butene. A solution of 0.125 g of β-hydroxy phosphonamide **3** ($R_1 = C_6H_5$; $R_2 = R_3 = CH_3$; $R_4 = H$) and 0.2 g of silica gel in 1.5 ml of toluene was heated at reflux for 15 hr. Vpc analysis of the product after dilution with ether and filtration indicated a 1.09:1.0 ratio of *cis*- and *trans*-2-phenyl-2-butenes. Using bromobenzene as an internal standard, the yield was determined to be 90%. The nmr spectrum of the olefinic mixture after removal of the solvent was in agreement with that reported for *cis*- and *trans*-2-phenyl-2-butenes.[17]

Reaction of α-Lithioethylphosphonic Acid Bis(dimethylamide) with Methyl Benzoate. General Method for the Preparation of β-Ketophosphonic Acid Bis(dimethylamides). To a stirred solution of 8.0 mmol of α-lithioethylphosphonic acid bis(dimethylamide) in 15 ml of tetrahydrofuran is added, while at −70° and under nitrogen, 0.544 g (4.0 mmol) of methyl benzoate. Stirring was continued for 2 hr at −70° and 0.5 hr at −70 to +25°. Water was then added and the tetrahydrofuran removed from the mixture by evaporation under vacuum. The aqueous solution was extracted with ether, and the combined ether extracts were washed extensively with 1 *N* sodium chloride solution to remove the unreacted ethylphosphonic acid bis(dimethylamide). Evaporation of the ether extracts after drying over magnesium sulfate afforded 0.840 g (79%) of keto phosphonamide **9** as an oil. The nmr spectrum ($CDCl_3$) showed a doublet of doublets at 1.50 (J_{HH} = 7, J_{HP} = 16, area 3), doublets at 2.59 and 2.65 (J = 10, 10, area 12), and multiplets at 4.3 (area 1), 7.45 (area 3), and 7.95 (area 2) ppm.

Reaction of α-Lithiooctylphosphonic Acid Bis(dimethylamide) with Methyl Pivalate. To a stirred solution of 10 mmol of α-lithiomethylphosphonic acid bis(dimethylamide) in 25 ml of tetrahydrofuran was added, while under nitrogen and at −70°, 2.261 g (10 mmol) of heptyl iodide. This solution was kept at −70° for 3 hr, and 6.25 ml (10 mmol) of 1.6 *M n*-butyllithium was then added. After stirring for 3 hr, 0.580 g (5.0 mmol) of methyl pivalate was added and stirring continued for 4 hr at −70° and 5 hr at room temperature. The unreacted octylphosphonic acid bis(dimethylamide) was recycled *in situ* by the following series of operations. The mixture was cooled to −70° and 3.1 ml (5.0 mmol) of *n*-butyllithium added. After stirring for 3 hr, 0.290 g (2.5 mmol) of methyl pivalate was added, and the mixture was stirred below −20° for 4 hr before quenching with water. The reaction mixture was

(17) M. Barbieux, N. Defay, J. Pecher, and R. H. Martin, *Bull. Soc. Chim. Belges*, 73, 716 (1964).

extracted with ether and the combined extracts washed with water, dried, and evaporated under vacuum to give 3.1 g of crude keto phosphonamide **11** as an oil. The nmr spectrum ($CDCl_3$) showed multiplets at 0.9, 1.3, 1.6, and 3.2 and a doublet at 2.62 (J = 10) ppm.

Preparation of β-Ketophosphonic Acid Bis(dimethylamide) (9) by Oxidation of the Corresponding β-Hydroxy Adduct. A stirred solution of 0.100 g (0.39 mmol) of β-hydroxyphosphonic acid bis(dimethylamide) (**3**, $R_1 = C_6H_5$; $R_2 = R_3 = H$; $R_4 = CH_3$) and 0.5 g of activated manganese dioxide (excess) in 4 ml of $CHCl_3$ was heated at reflux for 10 min. The manganese dioxide was then removed by filtration, and the solution was evaporated to give 90 mg (90%) of keto phosphonamide **9**, 97% pure by nmr analysis.

Reduction of β-Ketophosphonic Acid Bis(dimethylamide) (9). Synthesis of *trans*-1-Phenylpropene. To a stirred solution of 0.120 g (0.473 mmol) of β-ketophosphonic acid bis(dimethylamide) (**9**) in 3 ml of methanol was slowly added, while at 0°, 20 mg (excess) of sodium borohydride. After 1 hr of stirring, dilute hydrochloric acid was added to decompose the excess sodium borohydride, and the product was isolated by extraction with ether. The ether extracts were washed with water, dried, and evaporated under vacuum to afford 0.096 g (80%) of β-hydroxy phosphonamide **3** ($R_1 = C_6H_5$; $R_2 = R_3 = H$; $R_4 = CH_3$).

The crude product from above was heated at reflux in 3 ml of toluene containing 0.3 g of silica gel for 15 hr. Vpc analysis showed that *trans*-1-phenylpropene was produced in 98% purity. Using bromobenzene as an internal standard, the yield was estimated to be 92%.

Reduction of Ketophosphonic Acid Bis(dimethylamide) (11). Synthesis of *trans*-1-*t*-Butyl-1-nonene. The procedure of Eliel[13] for reductions using lithium aluminum hydride and aluminum chloride was followed. To a mixture prepared by stirring 0.402 g (3.0 mmol) of aluminum chloride and 0.032 g (0.86 mmol) of lithium aluminum hydride in 12 ml of ether for 0.5 hr at room temperature was added 0.600 g of a 3:1 mixture of β-keto phosphonamide **11** and octylphosphonic acid bis(dimethylamide). The resulting mixture was stirred for 2.5 hr and 0.5 ml of *t*-butyl alcohol then added to decompose the excess reagent. After 1 hr, 0.025 g more of the 3:1 mixture was added and the solution stirred for 30 hr at room temperature. Water was added, and the products were isolated by ether extraction. The ether extracts were washed with water, dried, and evaporated to give 0.432 g of a clear oil containing a trace of keto phosphonamide **11**, 5–10% *trans*-1-*t*-butylnonene (possibly formed during isolation), octylphosphonic acid bis(dimethylamide), and β-hydroxy phosphonamide **3** (R_1 = *t*-butyl; $R_2 = R_3 = H$; $R_4 = C_7H_{15}$).

Decomposition of 0.154 g of the above oil in refluxing toluene containing 0.3 g of silica gel gave a 94:6 ratio of *trans*- and *cis*-1-*t*-butylnonenes. Thermolysis of 0.250 g of the above product in refluxing benzene for 1.75 hr afforded pure *trans*-1-*t*-butylnonene in 71% yield by vpc analysis.

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Total Synthesis of Sativene

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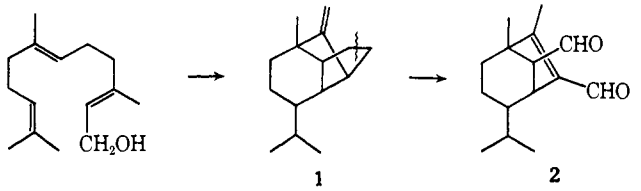
Abstract: A stereospecific total synthesis of the tricyclic sesquiterpene hydrocarbon, sativene (**1**), is described, and several interesting reactions are developed. A useful extension of the Grignard reaction is introduced whereby enolization can be suppressed in favor of addition by conducting the reaction at low temperature. A new method of protecting carbonyl groups toward hydroboration by formation of the 2,4-DNP derivative is reported, and an intramolecular alkylation [**16** → **17**] to construct the tricyclic carbon skeleton is described.

In a noteworthy display of chemical intuition, de Mayo, in 1962, suggested a pathway for the biogenesis of the then recently isolated sesquiterpene, helminthosporal, the toxin form *Helminthosporium sativum*.[1] The proposed pathway proceeded from farnesol *via* a relatively straightforward cyclization to the tricyclic sesquiterpene hydrocarbon **1**. **1** was then assumed to undergo oxidative cleavage of the indicated carbon–carbon bond to give helminthosporal (**2**).



1 **2**

At the time this prediction was made however, the carbon skeleton of **1** was unknown in sesquiterpene chemistry. In 1965, de Mayo and Williams provided strong support for this pathway when they were able to isolate small amounts of a sesquiterpene hydrocarbon, sativene, from *Helminthosporium sativum*, and to show that sativene did indeed possess the predicted structure, **1**.[2] We wish now to report the first, completely stereospecific, total synthesis of this unique sesquiterpene and to record a general method of entry into the tricyclic carbon skeleton.

Discussion and Results

An examination of Dreiding models of *cis*-decalin reveals that when ring B is in a boat conformation carbons **1** and **6** are quite close. Thus we considered that an interesting method for forming the ring system of sativene would be to synthesize a molecule such as **3** (where X = any leaving group) and to see if the requisite bond could be formed by an intramolecular alkylation.[3]

There are some interesting stereochemical problems associated with the synthesis of **3** (X = OTs) which

(1) P. de Mayo, R. Robinson, E. Y. Spencer, and R. W. White, *Experientia*, **18**, 359 (1962).

(2) P. de Mayo and R. E. Williams, *J. Am. Chem. Soc.*, **87**, 3275 (1965).

(3) There are several reports in the literature of various successful intramolecular alkylations, for example the notable synthesis of copaene: C. H. Heathcock, R. A. Badger, and J. W. Patterson, *ibid.*, **89**, 4133 (1967). No case similar to that reported here has been published however.