the error range was ±6% in each case. An important difference, however, was that ^{13}C NMR spectroscopy required a longer period of signal averaging to give a spectrum of lower signal/noise ratio than was needed to produce the edited ^{1}H spectrum. The potential is clear for using ^{1}H NMR more generally to follow ^{13}C (or ^{15}N) in biosynthetic research. Not only does this technique offer greater sensitivity (by about an order of magnitude) but the accuracy of cancellation of the unwanted resonances is such that quantitative determinations can be made.

Still further increases in sensitivity (or savings of time) are, in principle, obtainable. A reduction by a factor of 4 in the time required to obtain a given signal/noise ratio could be achieved if the pulse sequence used here were supplemented with ^{13}C broadband decoupling during ^{1}H data acquisition; the spectrum would also appear as a set of singlets. Pulse programmer control would need to be available for both pulse and decouple steps using the ^{13}C excitation channel; most commercial spectrometers lack this facility, and the filling of this gap will further extend the power of isotopic work with ^{13}C.

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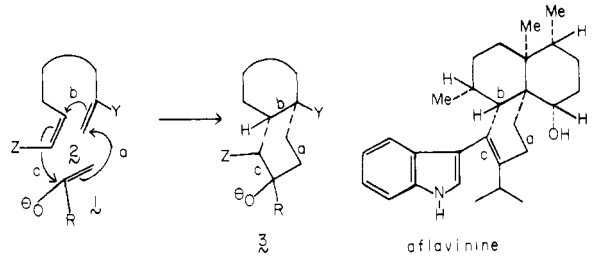
A Stereospecific 2 + 2 + 2 Annulation

Summary: A new strategy for multiple annulation involving sequential Michael and Aldol reactions is described.

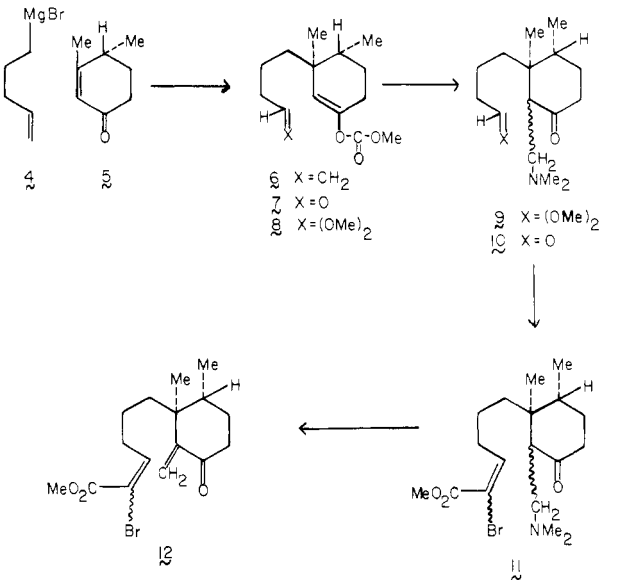
Sir: A tantalizing possibility for assembling polycyclic systems would utilize arrays bearing several centers of electrophilicity. A successful nucleophilic attack generates a new nucleophile that can, in principle, react with another intramolecular electrophile. The synthesis of fused, bridged, and spiro ring systems falls within the scope of this formalism. A proposed synthesis of the novel indolic sesquiterpene aflavinine[1,2] encouraged us to probe the



feasibility of an approach wherein enolate **1** reacts with bis(electrophile) **2**. A sequence of two Michael reactions (see arrows a and b) followed by an aldol reaction (arrow c) is projected to lead to the bicyclic product **3** (see connecting bonds a–c in structure **3** and the corresponding bond possibilities in aflavinine).

The usefulness of the scheme would depend on the efficacy of control elements in the multifaceted ensemble. The initial nucleophile must be directed to the desired electrophilic center. Proton transfers, which might undermine regioconnectivity, are to be avoided. Needless to say, utility will also be closely coupled to the degree of stereoselectivity that pertains. Below we report an experimental realization of such a conjecture.

Reaction of the Grignard reagent **4** with **5** (in 1:1 ether–DMS mediated by CuI) and trapping with methyl chloroformate afforded **6** in 72% yield.[3,4] Compound **6**



was converted to the desired substrate **12** in a six-step sequence in ca. 33% yield. The sequence starts with the previously described selective ozonolysis of the terminal olefin in the presence of the weakly nucleophilic enol carbonate linkage. The aldehyde **7** was converted to its dimethyl acetal **8**.[5] The required lithium enolate, which was exposed by the action of **8** with 3.5 equiv of methyllithium (THF; −78 °C)[6,7], reacts with freshly prepared [(dimethylamino)methylene]ammonium chloride[8] (−78 °C → room temperature) to afford **9**. Crude aldehyde **10**, which was obtained (0.65 N HCl; 15 min, room tempera-

(1) Gallagher, R. G.; McCabe, T.; Hirotsu, K.; Clardy, J.; Nicholson, J.; Wilson, B. J. *Tetrahedron Lett.* **1980**, *21*, 243.
(2) Cole, R. J.; Dorner, J. W.; Springer, J. P.; Cox, R. H. *J. Agric. Food Chem.* **1981**, *29*, 293.
(3) Danishefsky, S.; Kahn, M.; Silvestri, M. *Tetrahedron Lett.* **1982**, *23*,703. Upon scale-up, the yield falls to 72%.
(4) Danishefsky, S.; Kahn, M.; Silvestri, M. *Tetrahedron Lett.* **1982**, *23*, 1419.
(5) Satisfactory NMR, IR, and mass spectra were obtained on all new compounds. Representative data are given below. **8**: ^{1}H NMR (90 MHz, $CDCl_3$) δ 0.90 (s, 3 H), 0.90 (d, J = 6 Hz, 3 H), 1.00–2.40 (m, 11 H), 3.31 (s, 6 H), 3.70 (s, 3 H), 4.32 (t, J = 6 Hz, 1 H), 5.20 (s, 1 H); IR (neat) 1745 cm^{-1}. **11**: ^{1}H NMR (90 MHz, $CDCl_3$) δ 0.79 (s, 3 H), 1.00 (d, J = 6 Hz, 3 H), 2.16 (s, 6 H) 1.10–2.60 (m, 14 H), 3.80 (s, 3 H), 6.65 (t, J = 7.5 Hz 0.4 H), 7.26 (t, 7.5 Hz, 0.6 H); IR ($CHCl_3$) 1708, 1720 cm^{-1}. **12**: ^{1}H NMR (90 MHz, $CDCl_3$) δ 1.03 (s, 3 H), 0.80–2.70 (m, 14 H), 3.80 (s, 3 H), 5.08 (s, 1 H), 5.81 (s, 1 H), 6.61 (t, J = 7.5 Hz, 0.4 H), 7.24 (t, J = 7.5 Hz, 0.6 H); IR ($CHCl_3$) 1690, 1720 cm^{-1}. **15**: ^{1}H NMR (270 MHz, $CDCl_3$) δ 0.66 (d, J = 7.0 Hz, 3 H), 0.78 (d, J = 7.0 Hz, 3 H), 0.94 (s, 3 H), 0.95 (d, J = 7.0 Hz, 3 H), 0.60–2.40 (m, 16 H), 3.04 (m, 1 H), 3.72 (s, 3 H); IR ($CHCl_3$), 3550, 1715 cm^{-1}. **16** (major diastereomer): ^{1}H NMR (270 MHz, $CDCl_3$) δ 0.61 (s, 3 H), 0.76 (d, J = 7.0 Hz, 3 H), 0.81 (d, J = 6.6 Hz, 3 H), 0.99 (d, J = 7.0 Hz, 3 H), 1.00–2.00 (m, 12 H), 2.20 (m, 1 H), 2.40–2.70 (m, 2 H), 3.24–3.40 (m, 2 H), 3.76 (s, 3 H); IR ($CHCl_3$) 1690, 1720, 1740 cm^{-1}. **16** (minor diastereomer): ^{1}H NMR (270 MHz, $CDCl_3$) δ 0.55 (s, 3 H), 0.76 (d, J = 7.0 Hz, 3 H), 0.93 (d, J = 7.0 Hz, 3 H), 0.97 (d, J = 7.0 Hz, 3 H), 1.00–2.25 (m, 14 H), 2.55 (m, 1 H), 2.87–3.00 (m, 1 H), 3.26 (dd, J = 12, 3.5 Hz, 1 H), 3.75 (s, 3 H); IR ($CHCl_3$) 1695, 1725 cm^{-1}. **17**: ^{1}H NMR (270 MHz, $CDCl_3$) δ 0.64 (s, 3 H), 0.85 (d, J = 6.75 Hz, 3 H), 1.06 (d, J = 6.75 Hz, 3 H), 1.08 (d, J = 6.75 Hz, 3 H), 0.80–2.90 (m, 15 H), 3.50–3.70 (m, 2 H), 9.10 (s, 1 H); IR ($CHCl_3$) 1680, 1640 cm^{-1}.
(6) Cf.: Danishefsky, S.; Kitahara, T.; McKee, R.; Schuda, P. F. *J. Am. Chem. Soc.* **1976**, *98*, 6715.
(7) Holy, N. L.; Wang, U. F. *J. Am. Chem. Soc.* **1977**, *99*, 944.
(8) Kinast, G.; Tietze, L. F. *Angew. Chem., Int. Ed. Engl.* **1976**, *15*, 239.

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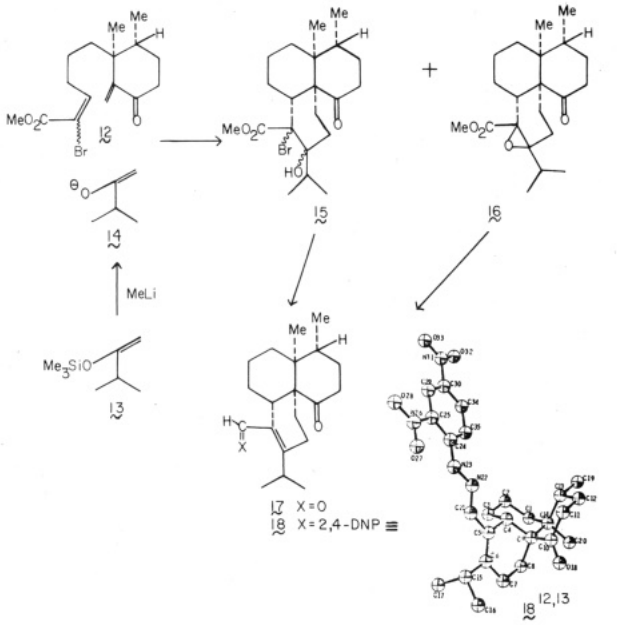
Scheme I



ture) from **9**, reacts with the sodium salt of methyl (dimethylphosphinyl)bromoacetate[9] in 1,2-dimethoxyethane to afford **11**. Treatment of **11** with *m*-chloroperoxybenzoic acid gives rise to **12** as a 2:3 mixture of *E* and *Z* isomers.

Reaction of silyl enol ether **13** (3.5 equiv) at −78 °C in 1,2-dimethoxyethane with methyllithium (2.5 equiv) generates, presumably, enolate **14**, which reacts with the esters **12** (−78 °C (30 min) → room temperature (1 h)). Chromatography on silica gel afforded three products (Scheme I). The least polar product (25%) corresponds to a bromohydrin,[5] formulated as structure **15**.[10] The other two products (15% combined, in a 4:1 ratio) are the epoxides **16**.[11] The major less polar epoxide melts from 138 to 139 °C, while the minor isomer melts from 142 to 143 °C.

That the bromohydrin **15** and the epoxides **16** contain the cis–cis stereochemistry (required for aflavinine) was demonstrated by their conversion to the same keto enal **17**. For **15**, this transformation was accomplished (44%) by reaction with lithium aluminum hydride in ether followed by oxidation with bis(pyridinium) dichromate in methylene chloride. Compound **17** was also obtained (51%) from the major epoxide **16** by the following sequence: (i) Red-Al–THF (Aldrich); (ii) pyridinium chlorochromate; (iii) Me_3SiI–carbon tetrachloride.

The structure of **17** was confirmed by X-ray crystallographic analysis[12,13] of its derived 2,4-dinitrophenylhydrazone, mp 243–244 °C dec.

Enlargements upon this theme and applications to the solution of various problems in total synthesis are receiving continuing attention in our laboratory.

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Registry No. **4**, 1119-51-3; **5**, 10463-42-0; **6**, 82343-62-2; **7**, 82343-65-5; **8**, 87011-65-2; **9**, 87011-66-3; **10**, 87011-67-4; **11**, 87011-68-5; (*E*)-**12**, 87011-69-6; (*Z*)-**12**, 87068-06-2; **13**, 17510-45-1; **15**, 87011-70-9; **16** (isomer 1), 87011-71-0; **16** (isomer 2), 87068-07-3; **17**, 87011-72-1; **18**, 87011-73-2.

Supplementary Material Available: Tables containing fractional coordinates, temperature factors, bond distances, and bond angles are compound **18** (5 pages). Ordering information is given on any current masthead page.

(9) Wadsworth, W. S., Jr.; Emmons, W. D. *J. Am. Chem. Soc.* **1961**, *83*, 1733.

(10) The stereochemistry of the hydroxyl and bromine and functions of the bromohydrin are unassigned.

(11) The sterochemistry of the oxirane ring is unassigned.

(12) Suitable crystals for X-ray diffraction formed from a methylene chloride/methanol mixture with symmetry $P2_1/c$. Preliminary experiments gave cell parameters of a = 12.860 (1) Å, b = 10.574 (3) Å, c = 19.108 (2) Å, and β = 106.91 (1)° for Z = 4. An automatic four-circle diffractometer equipped with a sealed-tube Cu X-ray source (λ = 1.5418 Å) and graphite monochromator was used for data collection. Of the 3573 reflections measured with $2\theta \leq 114°$, 2447 were observed ($I \geq 3\sigma I$). A multisolution tangent formula approach[13] to the phase solution gave an initial model, which was subsequently refined by using full-matrix least-squares techniques. Hydrogens were added with fixed isotropic temperature factors. The function minimized was $\sum\omega(|F_o| - |F_c|)^2$ with $\omega = (1/\sigma F_0)^2$ to give a final unweighted residual of 0.040. All intramolecular bond distances and angles are within normal ranges, and there are no abnormally short intermolecular contacts. Figure **18** is a perspective drawing showing the relative configuration of **18**. Tables I–III containing the final X-ray parameters, bond distances, and bond angles are provided as supplementary material.

(13) The following library of crystallographic programs was used: MULTAN 80, University of York, York, England, 1980; Structure Determination Package V17.0, Enraf-Nonius Corporation, Delft, Holland, 1981; ORTEP-II, Oak Ridge National Laboratory, Oak Ridge, TN, 1970.

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Phosphine- and Phosphite-Mediated Difluorocarbene Exchange Reactions of (Bromodifluoromethyl)phosphonium Salts.[1] Evidence for Facile Dissociation of (Difluoromethylene)triphenylphosphorane

Summary: (Bromodifluoromethyl)triphenylphosphonium bromide undergoes facile exchange of the bromodifluoromethyl group with tertiary phosphine and trialkyl phosphite. A mechanism that involves formation of the difluoromethylene ylide and dissociation of the ylide into difluorocarbene and triphenylphosphine is proposed to account for the observed exchange processes.

Sir: Phosphonium ylide formation by capture of electrophilic carbenes with nucleophilic tertiary phosphines is a well-established synthetic method[2] and has been recently shown to be a symmetry-breaking allowed pathway to ylides.[3] To our knowledge, however, no evidence has been presented to demonstrate the reverse process, namely, dissociation of a phosphonium ylide into carbene and tertiary phosphine.

We now report that (difluoromethylene)triphenylphosphorane (**3**), generated by the reaction of (bromodifluoromethyl)triphenylphosphonium bromide (**1**) with

(1) Presented in part at the 10th International Symposium on Fluorine Chemistry, Vancouver, Canada, August 1982, Abstract O-5.

(2) Speziale, A. J.; Marco, G. T.; Ratts, K. W. *J. Am. Chem. Soc.* **1960**, *82*, 1260. Speziale, A. J.; Ratts, K. W. *Ibid.* **1962**, *84*, 854. Burton, D. J.; Naae, D. G. *Synth. Commun.* **1973**, *3*, 197. Naae, D. G.; Kesling, H. S.; Burton, D. J. *Tetrahedron Lett.* **1975**, 3789. Tyuleneva, V. V.; Rokhlin, E. M.; Knunyants, I. L. *Russ. Chem. Rev.* (*Engl. Transl.*) **1981**, *50*, 280.

(3) Trinquier, G.; Malrieu, J. P. *J. Am. Chem. Soc.* **1979**, *101*, 7169.

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