over 3 min and after 20 min water was added and the mixture was allowed to warm to room temperature. Acidification of the aqueous phase to pH 3.5, after extraction with ethyl acetate to remove nonacidic materials, and extraction with ethyl acetate yielded, after drying ($MgSO_4$) and concentration under reduced pressure, 29.6 mg (98.7%) of prostaglandin $F_{2\alpha}$ (**3**) as a colorless oil, $[\alpha]^{25}D$ +23.9° (*c* 0.955, THF), exhibiting infrared and nmr (100 MHz) spectra and tlc behavior (in six solvent systems with silica gel and silica gel–$AgNO_3$ as adsorbants) identical with that of a sample of pure prostaglandin $F_{2\alpha}$.

The conversion of prostaglandin $E_2$ to $E_1$, which in conjunction with the E → $F_\alpha$ reduction described above would make possible the selective synthesis from prostaglandin $E_2$ of the three prostaglandins $E_1$, $F_{2\alpha}$, and $F_{1\alpha}$, has also been accomplished in a straightforward way. We have reported previously that the 11,15-bistetrahydropyranyl derivative of prostaglandin $F_{2\alpha}$ (**4**) can be selectively hydrogenated over Pd/C at the $\Delta^5$ olefinic bond to give the corresponding $F_{1\alpha}$ derivative.[8] The success of this reduction depends to a considerable extent on the steric screening of the $\Delta^{13}$ linkage by the 11- and 15-tetrahydropyranyl groups. It now appears that the dimethylisopropylsilyl (DMIS) grouping is even more effective than is tetrahydropyranyl in promoting selective reduction of the $\Delta^6$ over the $\Delta^{13}$ olefinic linkage. In addition, this silyl group is readily introduced and removed, even in the sensitive E series, which enhances still further its utility.

Reaction of prostaglandin $E_2$ (63 mg) in a little dry tetrahydrofuran with an excess of a 1:1 mixture of dimethylisopropylchlorosilane[9] and 1,1,3,3-tetramethyl-1,3-diisopropyldisilazane[10] at 25° for 48 hr produced the 11,15-bis-DMIS ether of prostaglandin $E_2$ DMIS ester in 97.4% yield as a colorless liquid which was homogeneous by tlc analysis. A solution of this substance (54 mg) in methanol at −23° was stirred with 5% palladium/charcoal catalyst (Engelhard Industries) under 1 atm of hydrogen until no starting material could be detected by tlc analysis (using silica gel impregnated with silver nitrate) (*ca.* 4 hr). Removal of catalyst and methanol and treatment with 3:1 acetic acid–water at 35° for 10 min gave after dilution with water, extraction, and evaporation almost pure prostaglandin $E_1$ (by tlc analysis) in an analytical yield (by conversion to prostaglandin $B_1$ and spectroscopic analysis[11]) of 102 ± 10%. Three recrystallizations of this material from ethyl acetate–cyclohexane gave very pure prostaglandin $E_1$ (22 mg, 77% yield), mp 115–115.5° (undepressed upon admixture with an authentic sample), $[\alpha]^{25}D$ −58.3°, $[\alpha]^{25}_{578}$ −61.7° (*c* 0.47, THF), which was spectroscopically (nmr, infrared) identical with pure prostaglandin $E_1$. Additional prostaglandin $E_1$ could be obtained from the mother liquors after chromatography.[12] It should be noted that the acid-catalyzed cleavage of the DMIS ethers occurs under markedly milder conditions (generally 3:1 acetic acid–water, 35°, 10 min) than are required for tetrahydropyranyl ethers. We have found this property to be useful in other studies in the prostaglandin area.[13] It has also been observed[13] that DMIS ethers are frequently nicely crystalline substances whereas the corresponding THP ethers are usually oils (additional chiral center!). We have not studied other bulky silyl derivatives extensively, but it is obvious that there are probably several besides the DMIS series which will prove useful because of the range of properties which can be obtained.

As a result of the present study any stereoselective synthesis of prostaglandin $E_2$ can also be considered as a stereoselective route to prostaglandins $E_1$, $F_{1\alpha}$, and $F_{2\alpha}$.

**Acknowledgment.** This research was assisted financially by grants from the U. S. Agency for International Development and the National Institutes of Health.

(8) E. J. Corey, R. Noyori, and T. K. Schaaf, *J. Amer. Chem. Soc.*, **92**, 2586 (1970).

(9) Prepared from dimethyldichlorosilane (small excess) and isopropyllithium.

(10) Prepared from dimethylisopropylchlorosilane and dry ammonia in ether. See C. C. Sweeley, R. Bentley, M. Makita, and W. W. Wells, *J. Amer. Chem. Soc.*, **85**, 2497 (1963).

(11) N. H. Andersen, *J. Lipid Res.*, **10**, 320 (1969).

(12) The reduction at $\Delta^5$ of the 11,15-bistetrahydropyranyl ether of prostaglandin $E_2$ is considerably less selective than that of the dimethylisopropylsilyl (DMIS) derivative reported above and also less selective than that observed[8] with the 11,15-bistetrahydropyranyl ether of prostaglandin $F_{2\alpha}$ (**4**).

(13) Unpublished work with Dr. A. Venkateswarlu.

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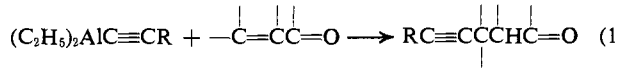
## The Reaction of Diethylalkynylalane Reagents with Conjugated Enones. A Method for 1,4 Addition of Acetylene Units to Simple α,β-Unsaturated Ketones

*Sir:*

γ,δ-Acetylenic ketones are valued synthetic intermediates since they are easily converted to a variety of important structural classes (*inter alia*, 1,4-diketones,[1] 1,5-dienes[2]). Although the conceptually most direct approach for their synthesis involves a Michael-type reaction between an acetylenic unit and a conjugated enone, in practice, all attempts to carry out this transformation have been unsuccessful.[3,4] This communication describes a new reaction which fills this gap in methodology (eq 1): diethylalkynylalanes react with a range



$$(C_2H_5)_2AlC{\equiv}CR + -\overset{|}{C}{=}\overset{|}{C}\overset{|}{C}{=}O \longrightarrow RC{\equiv}C\overset{|}{C}\overset{|}{C}\overset{|}{H}C{=}O \quad (1)$$

of simple conjugated enones to give fair–excellent yields of 1,4-addition products.[5]

(1) G. Stork and R. Borch, *J. Amer. Chem. Soc.*, **86**, 935 (1964).

(2) W. S. Johnson, N. P. Jensen, J. Hooz, and E. J. Leopold, *ibid.*, **90**, 5872 (1968).

(3) (a) A review of this problem appears in the Ph.D. Thesis of J. H. Rea, University of Missouri, 1965; *Diss. Abstr.*, **26**, 5043 (1966). (b) Dilithium trialkynylcuprate complexes also fail to effect the conjugate addition of an alkynyl group to a conjugated enone: H. O. House and W. F. Fischer, Jr., *J. Org. Chem.*, **34**, 3615 (1969).

(4) In contrast, the conjugate addition reactions of alkyl, vinyl, and aryl Grignard reagents or organocopper species are part of standard synthetic repertoire: (a) M. S. Kharasch and O. Reinmuth, "Grignard Reactions of Non-metallic Substances," Prentice-Hall, New York, N. Y., 1954, Chapter 6; (b) H. O. House and W. F. Fischer, Jr., *J. Org. Chem.*, **33**, 949 (1968); (c) E. J. Corey and J. A. Katzenellenbogen, *J. Amer. Chem. Soc.*, **91**, 1851 (1969); (d) J. Hooz and R. B. Layton, *Can. J. Chem.*, **48**, 1626 (1970).

(5) A model for the development of this method was the Nagata hydrocyanation reaction (W. Nagata and M. Yoshioka, *Tetrahedron Lett.*, 1913 (1966)), in which the sp-hybridized carbon of a cyano function is delivered to the β carbon of a conjugated enone. This reaction prompted the expectation that an alkynyl group might behave similarly.

**Table I.** The Conjugate Addition of Acetylenic Groups to Simple $\alpha,\beta$-Unsaturated Ketones

$$Et_2AlC{\equiv}CR + -\overset{|}{C}{=}\overset{|}{C}\overset{|}{C}{=}O \longrightarrow RC{\equiv}C\overset{|}{C}\overset{|}{C}\overset{|}{H}C{=}O$$

| R | Ketone | Reaction time, hr, and temp, °C | Solvent,[a] ratio by volume | Product,[b] % yield[c,d] |
|---|---|---|---|---|
| $n$-$C_4H_9$ | 1-Acetylcyclohexene | 1, 0 | E–L, 1:10 | 2-(1-Hexynyl)acetylcyclohexane, 79[c] |
| $C_6H_5$ | 1-Acetylcyclohexene | 1.5, −15 | E–L, 1:10 | 2-(Phenylethynyl)acetylcyclohexane, 71[c] |
| $C_6H_5$ | 1-Acetylcyclohexene | 1.25, −15 | E–L, 3:1 | 2-(Phenylethynyl)acetylcyclohexane, 94[c] |
| $C_6H_5$ | 1-Acetylcyclohexene | 1.25, −15 | T–L, 2:1 | 2-(Phenylethynyl)acetylcyclohexane, 3[c,e] |
| $C_6H_5$ | Benzalacetone | 1.5, −10 | E–L, 1:15 | 4,6-Diphenylhex-5-yn-2-one, 95[c] |
| $n$-$C_4H_9$ | Benzalacetophenone | 0.75, 5 | E–L, 1:4 | 1,3-Diphenylnon-4-yn-1-one, 65[d] |
| $C_6H_5$ | Benzalacetophenone | 1.5, 25 | E–L, 1:10 | 1,3,5-Triphenylpent-4-yn-1-one, 81[d] |
| $n$-$C_4H_9$ | Methyl vinyl ketone | 1.5, −15 | E–L, 1:12 | Dec-5-yn-2-one, 48[c] |
| $C_6H_5$ | 3-Methylbut-3-en-2-one | 1.5, −15 | E–L, 1:12 | 3-Methyl-6-phenylhex-5-yn-2-one, 50[c] |
| $C_6H_5$ | Pent-3-en-2-one | 1, −10 | E–L, 1:12 | 4-Methyl-6-phenylhex-5-yn-2-one, 54[c] |
| $n$-$C_4H_9$ | Mesityl oxide | 4, 25 | E–L, 1:10 | 4,4-Dimethyldec-5-yn-2-one, 30[c,f] |

[a] E = ether, L = ligroin, T = tetrahydrofuran. [b] Products were analyzed by vpc, isolated, and characterized by spectroscopic methods (compatible ir, nmr, and mass spectral data) and satisfactory elemental analyses. [c] By vpc analysis. [d] Purified product, isolated by distillation or crystallization. [e] Predominantly 1,2-addition product is obtained. [f] Approximately 40% 1,2 addition occurs.

The requisite mixed organoalane is easily prepared[6] by converting the appropriate terminal acetylene into the lithium derivative (using $n$-butyllithium), and treating the resultant mixture with diethylaluminum chloride (eq 2). The supernatant containing the alane reagent

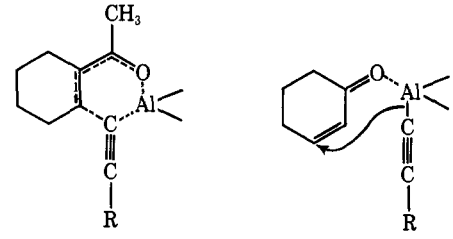
$$RC{\equiv}CLi + (C_2H_5)_2AlCl \longrightarrow (C_2H_5)_2AlC{\equiv}CR + LiCl \quad (2)$$

(2 equiv) is treated with an $\alpha,\beta$-unsaturated ketone (1 equiv)[7] to give, after suitable processing, the $\gamma,\delta$-alkynyl ketone.[8,9] The scope of this new process, illustrated by the reaction between several representative enones with 1-hexyne and phenylacetylene, is summarized in Table I.

The success of the reaction depends critically on the proper selection of experimental conditions.[11] Trial experiments indicated that an ether–ligroin solvent system usually gave acceptable results, but exhaustive attempts to optimize each run have not been made. The significant effect of solvent is illustrated by comparison of entries 3 and 4 of Table I. The 94% yield of conjugate addition product observed in an ether-rich solvent mixture (entry 3) is reduced to *ca.* 3% in tetrahydrofuran (entry 4).

The reaction is restricted to ketones capable of adopting a cisoid conformation. Cyclic ketones in which the enone system is rigidly constrained to a transoid geometry, such as 2-cyclohexenone or isophorone, react with the alane reagent to provide the tertiary carbinol (80–85%) derived from 1,2 rather than 1,4 addition of the acetylenic unit.

A plausible pathway involves the intramolecular delivery of an alkynyl group through a six-membered transition state depicted in idealized form by **1**. Thus, 1,4



**1** **2**

addition occurs when structural circumstances enable the incorporation of the necessary syn geometry (as in acyclic enones or acetylcyclohexene), **1**, but in cases involving transoid enones (cyclohexenone, etc.), geometric constraints (idealized by **2**) operate to prohibit conjugate addition, and 1,2 addition supervenes.[12]

$\alpha,\beta$-Ethylenic aldehydes and $\alpha,\beta$-acetylenic ketones, such as cinnamaldehyde and phenylacetylacetylene, likewise react with the mixed alane reagent (from phenylacetylene) to provide, in good yield, the products of 1,2 addition of the phenylethynyl group.

Despite these limitations, it is evident that this new alkylation method—in view of its simplicity and directness—offers advantages over current multistep approaches for the construction of $\gamma$-ketoacetylenes. An illustration of its utility for the elaboration of substituted cyclopentenones follows the description of a typical experimental procedure.

**1,3,5-Triphenylpent-4-yn-1-one.** All operations were carried out under a nitrogen atmosphere. To a solution of 8.16 g (80 mmol) of phenylacetylene in 120 ml of olefin-free dry ligroin was added 47 ml of a 1.7 *N* solution of $n$-butyllithium in hexane (Foote Mineral Co.), main-

(6) J. Fried, C.-H. Lin, and S. H. Ford, *Tetrahedron Lett.*, 1379 (1969).

(7) A 1:1 ratio of organoalane to enone may be used; however, longer reaction times or higher temperatures are necessary to achieve reasonable yields of products.

(8) The product of 1,2 addition is also formed in some cases—the highest amount observed was 40% (entry 11, Table I). Attempts to assay accurately the per cent 1,2-addition product was hampered, in many cases, by the instability of the resulting carbinols.

(9) No evidence was obtained for transfer of an ethyl group (either 1,2- or 1,4-). These results, together with a preceding body of evidence, demonstrate the remarkably selective nature of mixed organoalanes and alanates (dialkylalkynyl and di- and trialkylalkenyl) in reactions with electrophilic functionality. Invariably, carbon–carbon bond formation occurs involving "transfer" of that group bonded to aluminum possessing the highest degree of s character.[6,10]

(10) G. Zweifel, J. T. Snow, and C. C. Whitney, *J. Amer. Chem. Soc.*, **90**, 7139 (1968).

(11) The crucial role of proper choice of reaction variables in determining the success of various coupling and condensation processes has recently been emphasized: *cf.* E. J. Corey and G. H. Posner, *J. Amer. Chem. Soc.*, **90**, 5615 (1968); E. J. Corey and J. A. Katzenellenbogen, *ibid.*, **91**, 1851 (1969); H. C. Brown, M. M. Rogić, H. Nambu, and M. W. Rathke, *ibid.*, **91**, 2147 (1969); E. J. Corey and I. Kuwajima, *ibid.*, **92**, 395 (1970); C. J. V. Scanio and R. M. Starrett, *ibid.*, **93**, 1539 (1971).

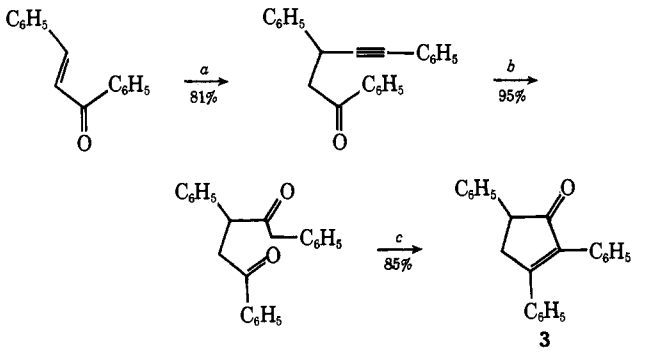
(12) Analogous proposals have appeared to explain the failure of prior attempts to effect conjugate addition of allylic Grignard reagents to cyclic enones: L. Mandell and J. M. Brodmann, *J. Org. Chem.*, **31**, 591 (1966). Despite the conceptual similarity, the hydrocyanation process follows a different reaction pathway,[5] as does the conjugate addition of organocopper reagents to $\alpha,\beta$-unsaturated ketones.[4b,4d,13]

(13) H. O. House, W. L. Respess, and G. M. Whitesides, *ibid.*, **31**, 3128 (1966); C. P. Casey and R. A. Boggs, *Tetrahedron Lett.*, 2455 (1971).

taining the temperature below *ca.* 15°. After stirring the suspension for 15 min at 20°, 15 ml of dry ether was added. Then a solution of 80 mmol of diethylaluminum chloride (Alfa Inorganics, Inc.) in 20 ml of ligroin was added to the cooled (*ca.* 15°) suspension, followed by an additional 60 ml of ligroin. After stirring for 30 min at *ca.* 25°, the precipitate of LiCl was allowed to settle. To the decanted supernatant[14] was added a solution of 8.32 g (40 mmol) of benzalacetophenone in 15 ml of ether–ligroin (3:1) at 25°, and the mixture was stirred for 4 hr. After slowly pouring into a mixture of ice–concentrated HCl, the organic layer was cooled, and afforded, after crystallization, 10 g (81%) of 1,3,5-triphenylpent-4-yn-1-one, mp 93.5–94.5°. *Anal.* Calcd for $C_{23}H_{18}O$: C, 89.00; H, 5.85. Found: C, 88.78; H, 6.06.

Using benzalacetophenone as an example, the synthesis of cyclopentenone **3** by chain extension, specific hydration,[1] and cyclization (Scheme I), in 65% yield (with

**Scheme I**




**3**

[a] $Et_2AlC{\equiv}CC_6H_5$, $N_2$, 4 hr, 25°. [b] $HgSO_4$ (3 mol %), 4 drops of concentrated $H_2SO_4$, 10:1 EtOH–$H_2O$, 14-hr reflux. [c] NaOH (4%) in MeOH, $N_2$, 1-hr reflux.

isolation of each intermediate[15] and no attempt at optimization), demonstrates the usefulness of this method.[16] In concert with the Stork–Borch hydration method,[1] a variety of other useful structures (*e.g.*, furans, pyrroles) also become easily accessible from acetylene precursors.

**Acknowledgment.** We thank the National Research Council of Canada and the University of Alberta for financial support.

(14) The enone may be introduced directly into the heterogeneous reaction mixture without significantly diminishing the yield of conjugate addition product.

(15) See footnote *b*, Table I.

(16) For syntheses of *cis*-jasmone from γ-ketoacetylenes, see G. Stork and R. Borch, *J. Amer. Chem. Soc.*, **86**, 936 (1964); J. E. McMurry and T. E. Glass, *Tetrahedron Lett.*, 2578 (1971).

(17) Holder of a 1967 (Centennial) Science Scholarship.

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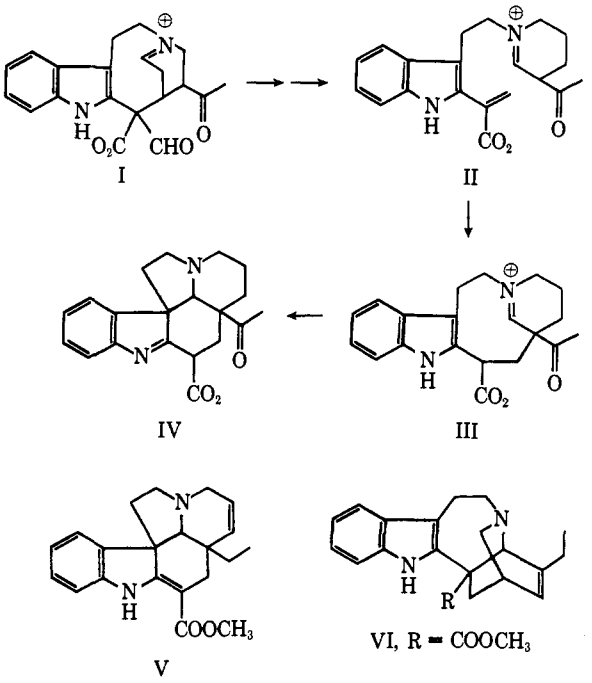
## Studies on Indole Alkaloid Biosynthesis. VII.[1] The Later Stages of Aspidosperma Alkaloid Biosynthesis

*Sir:*

Although numerous investigations on the earlier stages of Aspidosperma alkaloid biosynthesis are now available,[2] experimental data on many aspects of the later stages are as yet lacking. Wenkert[3] proposed that the Strychnos skeleton (I) was a precursor of the Aspidosperma series and invoked the intermediacy of appropriate acrylic acid (II) and nine-membered ring (III) intermediates in the overall conversion, Strychnos (I) → Aspidosperma (IV). Our previous investigations in *Vinca rosea* L.[4] and *Vinca minor* L.[5] plants suggested that the transannular cyclization III → IV did not appear to be a required *in vivo* pathway. On the other hand, in an elegant series of experiments in *V. rosea* seedlings,




Scott[6,7] provided support for Wenkert's implication of the Strychnos skeleton by demonstrating that stemmadenine, a reduced form of I, is incorporated into the Aspidosperma alkaloids. In our respective studies,[4,6] designed to attain rather different objectives, we were able to demonstrate the *in vivo* conversion, tabersonine (V, Aspidosperma) → catharanthine (VI, Iboga),[8] a process which required a substantial rearrangement of the tabersonine molecule. Attempts to rationalize these and other results[5–7] implicated the acrylic ester derivative VII as a possible intermediate in these biosynthetic conversions. It is clear that VII is a close relative of the intermediate II previously proposed by Wenkert and it also relates directly to the more recently isolated secodine family (for example, IX).[9–11] Bat-

(1) Part VI: J. P. Kutney, J. F. Beck, V. R. Nelson, and R. S. Sood, *J. Amer. Chem. Soc.*, **93**, 255 (1971).

(2) For a recent review, see A. I. Scott, *Accounts Chem. Res.*, **3**, 151 (1970).

(3) E. Wenkert, *J. Amer. Chem. Soc.*, **84**, 98 (1962).

(4) J. P. Kutney, W. J. Cretney, J. R. Hadfield, E. S. Hall, V. R. Nelson, and D. C. Wigfield, *ibid.*, **90**, 3566 (1968).

(5) J. P. Kutney, C. Ehret, V. R. Nelson, and D. C. Wigfield, *ibid.*, **90**, 5929 (1968).

(6) A. I. Scott, 2nd Natural Product Symposium, Jamaica, Jan 1968; A. A. Qureshi and A. I. Scott, *Chem. Commun.*, 948 (1968).

(7) A. I. Scott, P. C. Cherry, and A. A. Qureshi, *J. Amer. Chem. Soc.*, **91**, 4932 (1969).

(8) In a private communication, Professor Scott has informed us that they have confirmed our results concerning the conversion, tabersonine → vindoline and catharanthine in *V. rosea* plants (both *ca.* 0.05% incorporation).

(9) G. A. Cordell, G. F. Smith, and G. N. Smith, *Chem. Commun.*, 189, 191 (1970).

(10) R. T. Brown, G. F. Smith, K. S. J. Stapleford, and D. A. Taylor, *ibid.*, 190 (1970).

(11) A. R. Battersby and A. K. Bhatnagar, *ibid.*, 193 (1970).