phenyl isocyanide, 931-54-4; phenyl cyanide, 100-47-0; 2,6-dimethylpyridine, 108-48-5; dimethyl sulfide, 75-18-3; triethylphosphine, 554-70-1; bis(η^6-dibenzyl ether)chromium (0), 67775-55-7; 2-cycloheptylidenecycloheptanone-2,4-DNP, 73728-35-5; 2,6-bis(1-cyclohexenyl)cyclohexanone-2,4-DNP, 73728-36-6; nitrosobenzene, 586-96-9; aniline, 62-53-3; azobenzene, 103-33-3; azoxybenzene, 495-48-7; 2-azoxybiphenyl, 7334-10-3; 2-aminobiphenyl, 90-41-5; *N,N'*-dicyclohexylurea, 2387-23-7; *N,N'*-dicyclohexyloxamide, 3299-64-7.

Nickel-Catalyzed Conjugate Addition of Alkynyl Groups to α,β-Unsaturated Ketones

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The complex formed by reaction of $Ni(acac)_2$ and DiBAH (1:1) catalyzes conjugate addition of dialkylaluminum acetylides to α,β enones; on hydrolysis, 3-alkynyl ketones are produced in high yield. Through this procedure conjugate addition of alkynyl groups to either *S*-cis or *S*-trans enones can be effected. This procedure is the first one which permits conjugate addition of terminal alkynyl units to ordinary *S*-trans enones. In cases where more than one stereochemical outcome is possible, conjugate addition of alkynyl units gives only one of these. Only 1,4-addition is observed and this only of the alkynyl unit. Complications arising from oxygen substitution in the alkynyl side chain are described.

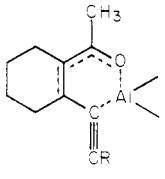
The conjugate addition of an alkynyl group to an α,β-unsaturated ketone has been a formidable synthetic challenge. Organocuprates, the most commonly used reagents for 1,4-addition of alkyl and alkenyl groups to α,β enones, cannot be employed in alkynylation reactions owing to the tenacity with which copper binds alkynyl ligands.[1] In fact, this inability of cuprates to transfer alkynyl groups has been used to advantage by Corey and Beames.[2] By the use of a mixed cuprate complex, $(RC{\equiv}C)R_tCuLi$, in which R_t represents the group to be transferred, they were able to circumvent the necessity of wasting one unit of the group R_t; in each case studied, where R_t = alkyl or alkenyl, the alkynyl group was never transferred.

Acetylenic alanes conjugately add their alkynyl units to α,β enones but only under certain circumstances. If the α,β-unsaturated ketone is able to achieve an *S*-cis conformation, it has been found that reaction 1 will then

$$(C_2H_5)_2AlC{\equiv}CR + C{=}C{-}C{=}O \xrightarrow{\text{ether}} RC{\equiv}C{-}C{-}CH{-}C{=}O \quad (1)$$

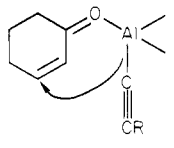
R = alkyl or phenyl

proceed in fair to excellent yield.[3] Cyclic ketones in which the enone system is rigidly constrained to a transoid geometry, such as 2-cyclohexenone, react with the alane reagent to give the tertiary carbinol (80–85%) derived from 1,2- rather than 1,4-addition of the acetylenic unit. A reasonable explanation for this reactivity mode involves the necessity for a six-membered transition state for conjugate addition (1). In cases involving transoid enones



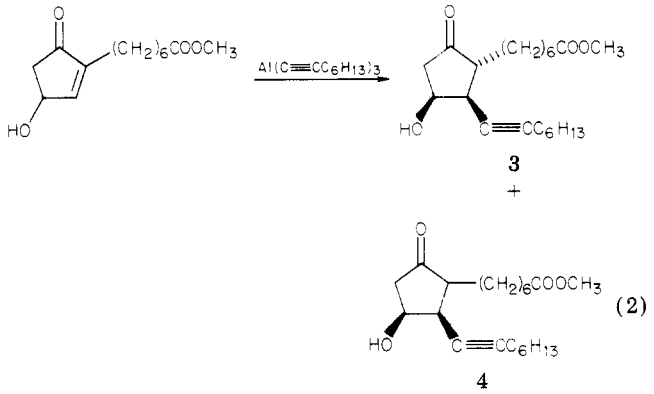
1

(e.g., cyclohexenone) geometrical restraints prohibit 1,4-addition, so that 1,2-addition occurs instead (2).



2

In their investigations into the application of 1,4-addition reactions to the synthesis of prostaglandins, Pappo et al.[4] were able to perform reaction 2 on a fixed *S*-trans



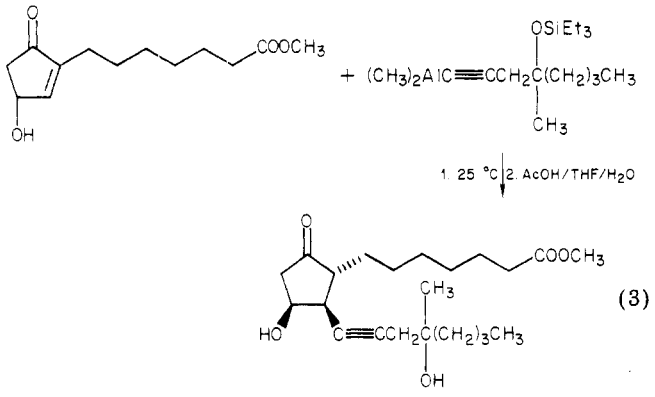
3 + 4 (2)

enone. Compounds **3** and **4** were obtained in approximately a 1:2 ratio. The fact that the entering octynyl group added cis to the hydroxy function indicates participation of that group in the 1,4-addition process by way of a five-membered cyclic intermediate analogous to structure **1**. Blockage of the hydroxy function by a tetrahydropyranyl group prevented reaction with the aluminum reagent. Pappo and co-workers[5] used this method of conjugate addition to obtain 11-epiprostaglandin derivatives in 40% yield (reaction 3).

The Pappo group[6] also demonstrated that a trialkynyl boron derivative would conjugatively add *one* of its alkynyl groups to an enone able to achieve an *S*-cis conformation. The following reaction proceeded to give adduct **5** in 48%

(1) House, H. O.; Fischer, W. F., Jr. *J. Org. Chem.* **1969**, *34*, 3615.
(2) Corey, E. J.; Beames, D. J. *J. Am. Chem. Soc.* **1972**, *94*, 7210.
(3) Hooz, J.; Layton, R. B. *J. Am. Chem. Soc.* **1971**, *93*, 7320.
(4) Pappo, R.; Collins, P. W. *Tetrahedron Lett.* **1972**, 2627.
(5) Collins, P. W.; Dajani, E. Z.; Bruhn, M. S.; Brown, C. H.; Palmer, J. R.; Pappo, R. *Tetrahedron Lett.* **1975**, 4217.
(6) Bruhn, M.; Brown, C. H.; Collins, P. W.; Palmer, J. R.; Dajani, E. Z.; Pappo, R. *Tetrahedron Lett.* **1976**, 235.

0022-3263/80/1945-3053$01.00/0 © 1980 American Chemical Society



(3)

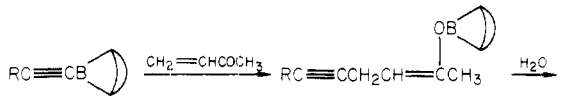
40% yield,
(±) mixture

yield after acid hydrolysis (reaction 4). Brown and co-

$$B(C{\equiv}CCH_2CH_2CH_2Cl)_3 \xrightarrow[2.\ H_3O^+]{1.\ CH_3C(O)CH{=}CH_2} CH_3C(O)(CH_2)_2C{\equiv}C(CH_2)_3Cl \quad (4)$$

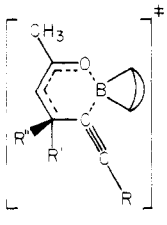
5

workers[7] have improved upon this general reaction so that it would be useful in cases where the acetylenic moiety is a valuable intermediate. The use of *B*-1-alkylyl-9-borabicyclo[3.3.1]nonanes avoids the waste of the two residual alkynyl units on the reagent used in reaction 4. The following reaction in pentane at room temperature gives high yields of 4-alkynyl-2-butanones with methyl vinyl ketone and related ketones able to adopt a cisoid conformation (reaction 5). As in the case of alkynylalanes,



$$RC{\equiv}CCH_2CH_2COCH_3 \quad (5)$$

transoid ketones gave no indication of the desired reaction. This observation and the fact that steric bulk at the β-position retarded the reaction led the authors to suggest a cyclic transition state analogous to the one proposed for the 1,4-addition reactions of alkynylalanes (**6**).



6

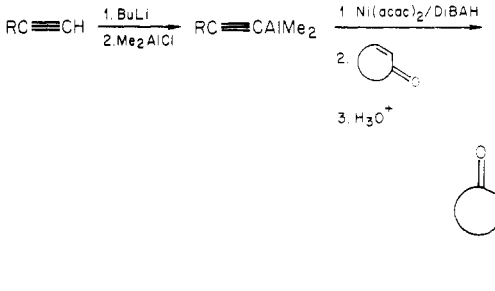
An indirect method of conjugate addition of an alkynyl group to a fixed *S*-trans enone without neighboring-group participation has been developed by Corey and Wollenburg.[8] This procedure involves addition of bis(tri-*n*-butylstannyl)ethylene by cuprate addition and subsequent oxidative elimination of a stannyl group to give, overall, conjugate addition of acetylide to the enone.

Each of the sequences which achieve conjugate addition of alkynyl units suffers from severe limitations. The enone substrate must be capable of an *S*-cis conformation or, alternatively, must have a conveniently located functional group for direction of an intramolecular attack by the organometallic reagent. For those enones which fit neither one of these requirements, it is only possible to conjugately add the ethynyl group, and this must be done by an indirect method. Since β-acetylenic ketones are valued synthetic precursors to important structural classes (e.g., 1,4-diketones[9] and 1,5-dienes[10]), it is clearly of interest to find an approach to their formation which is both general and direct.

A catalyst prepared from $Ni(acac)_2$ and diisobutylaluminum hydride had proven to be an exceedingly useful reagent for enabling the conjugate addition of alkenylzirconium complexes to α,β enones.[11] It was thus reasonable to assume that this same type of reactivity might be exploitable for conjugate addition of alkynyl groups as well. This conjugate addition reaction would circumvent the requirement for an enone to adopt an *S*-cis conformation or a group suitable for participation in a cyclic transition state since the nickel catalyst system is known to be effective on ordinary *S*-trans enones. We had demonstrated earlier[12] that dialkylaluminum alkenyls, in the presence of $Ni(acac)_2$/DiBAH, will transfer both alkenyl and alkyl groups to an α,β enone with an approximate ratio of 4:1. We attributed this selectivity to relative abilities of alkenyl vs. alkyl groups to transmetalate between Al and Ni; this transmetalation results, we believe, in the formation of the reactive transition-metal species which takes part in the conjugate addition step. We therefore selected dialkylalkynylalanes as the organometallic reagents for investigation as selective alkynylation reagents when used in conjunction with the reduced nickel catalyst system. We postulated that the difference in bridging ability for alkynyl vs. alkyl groups[13] would be large enough so that alkyl group transfer from the dialkylalkynylalane would not compete successfully with alkynyl group transfer. The use of such reagents should, as well, prove versatile since the requisite organoalane is easily prepared by converting the appropriate terminal acetylene into the lithium derivative and treating the resultant mixture with dialkylaluminum chloride. Such a conjugate addition sequence would be a significant improvement over the rather narrow scope of currently existing methods for attempting this transformation with alkynyl units.

Experimental Results and Discussion

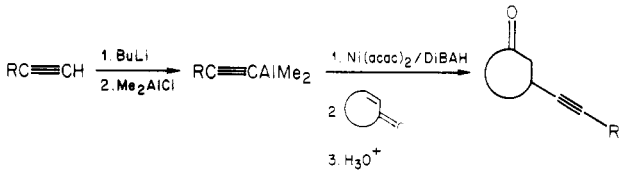
As we have reported earlier in a preliminary communication,[14] we found that the $Ni(acac)_2$/DiBAH system would indeed catalyze the conjugate addition of terminal alkynyl units from dialkylaluminum acetylides to both *S*-cis and *S*-trans enones (reaction 6). Typical results are

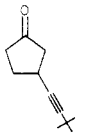
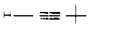
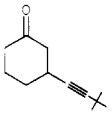
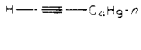
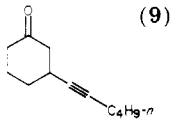
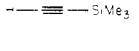
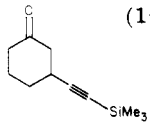
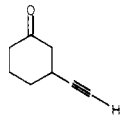
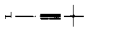
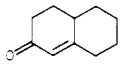
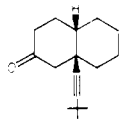
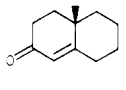
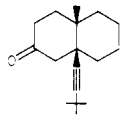
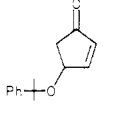
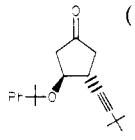
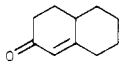
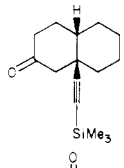
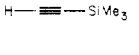
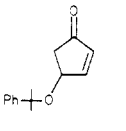
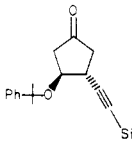


(6)

(7) Sinclair, J. A.; Molander, G. A.; Brown, H. C. *J. Am. Chem. Soc.* **1977**, *99*, 954.
(8) Corey, E. J.; Wollenburg, R. H. *J. Am. Chem. Soc.* **1974**, *96*, 5581.
(9) Stork, G.; Borch, R. *J. Am. Chem. Soc.* **1964**, *86*, 935.
(10) Johnson, W. S.; Jensen, N. P.; Hooz, J.; Leopold, E. J. *J. Am. Chem. Soc.* **1968**, *90*, 5872.
(11) Loots, M. J.; Schwartz, J. *J. Am. Chem. Soc.* **1977**, *99*, 8045.
(12) Carr, D. B. Ph.D. Dissertation, Princeton University, Princeton, NJ, 1978.
(13) Mole, T.; Jeffrey, E. A. "Organoaluminum Compounds"; Elsevier: Amsterdam, 1972; pp 276–7.
(14) Hansen, R. T.; Carr, D. B.; Schwartz, J. *J. Am. Chem. Soc.* **1978**, *100*, 2244.

Table I.

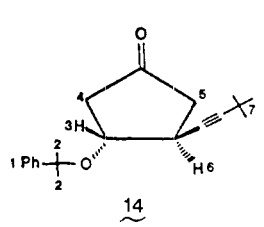


acetylene	α,β enone	product	ν(C≡C)Raman, cm⁻¹	yield,[a] %
		(7) 	2238	60
		(8)[e] 	2236	72
		(9)[e] 	2231	71
		(10)[e] 	2175	80[f]
		(11) 	2060	15[b]
		(12)[e] 	2231	67[c]
		(13)[e] 	2234	49[d]
		(14)[e] 	2238	85
		(15) 	2160	70[c]
		(16) 	2170	55

[a] Yields are isolated yields except where noted and have *not* been maximized except for **14**. [b] Compound **11** can be prepared approximately quantitatively from **15**.[15] ν(≡CH) = 3313 cm⁻¹. [c] Cis ring fusion was assigned by conversion of **15** to the terminal acetylene by cleavage with $(CH_3CH_2)_4NF$ and by subsequent reduction of the terminal acetylene [5% Pd/C, H_2 (1 atm)]. The resulting ketone was found to be identical by NMR, infrared, and gas chromatographic analysis with 9-ethyl-*cis*-2-decalone, prepared by the copper acetate catalyzed addition of ethyl Gringnard reagent to $\Delta^{1,9}$-octalone, a sequence which has been shown to afford cis ring fusion.[16] [d] Cis ring fusion is based on ^1H NMR data.[17] [e] Satisfactory analytical data (±0.4% for C and H) for this compound were submitted for review. [f] By VPC.

shown in Table I and demonstrate, in part, the scope of this reaction.

The procedure for effecting conjugate addition by this route is simple and straightforward and was optimized for compound **14**. To the $Ni(acac)_2$/DiBAH catalyst in ether at 0 °C is added a dialkylaluminum acetylide (easily available from the lithium acetylide and dialkylaluminum chloride) as a solution in ether. The reaction mixture is cooled to −5 °C, and the enone in ethereal solution is added dropwise over 15 min. The reaction is usually complete

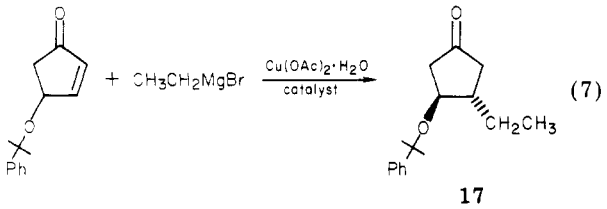


14

Figure 1. ^{1}H NMR spectral data for compound **14**. For position 2, the diastereotopic methyls here display slightly different shifts (separation 4 Hz). For position 3, this is not a true quartet; on expansion of signals it is possible to see some fine structure.

within 1 h at −5 °C, although in some cases longer reaction times result in higher yields. Only the acetylide group of the mixed alane was transferred, and in no case was 1,2-addition observed.

As may be seen from Table I, in cases where two stereochemical isomers are possible, conjugate addition of alkynyl units proceeds to give only one of these. For the alkoxy-substituted cyclopentenone, the product formed possessed the anti stereochemistry as shown by NMR (Figure 1). In particular, it has been shown by numerous examples (reactions 2 and 3, ref 4 and 5) that when hydroxy and acetylide groups are syn, the pattern for H-3 appears at δ 4.44 as a triplet ($J_{H_4H_{4'}-H_3}$ = 4 Hz) split into doublets ($J_{H_3-H_6}$ = 1 Hz). In contrast to this result, when these groups are known to be anti, the resonance for H-3 appears at δ 4.07 as a "quartet" with coupling constants approximately equal to 6 Hz.[18] This pattern is in keeping with the one shown in Figure 1. To further substantiate the assignment, the following reaction was performed in order to observe the splitting pattern for H-3 of product **17** (reaction 7). The copper-catalyzed conjugate addition



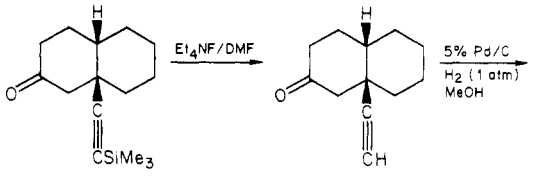
(7)

17

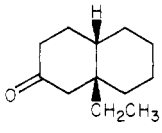
of a Grignard reagent to a 4-substituted α,β enone is a sequence which has been shown to afford anti stereochemistry.[19] The pattern for H-3 of **17** was a "quartet" at δ 3.63 with J = 5.6 Hz, in agreement with the assignment in **14** and **16**.

In the case of reaction with octalone systems (Table I, compounds **12**, **13**, and **15**), nickel-catalyzed conjugate addition of alkynyl groups proceeds to give only the product with cis ring fusion, a result which is analogous to that found for organocuprate conjugate additions to these systems.[19] The stereochemical assignment for compound **13** is based on ^{1}H NMR.[17] It has been found by careful measurement of NMR line widths at half-height ($W_{h/2}$) of angular methyl groups in *cis*- and *trans*-decalins that an unequivocal assignment of the stereochemistry of the A,B ring juncture can be made on this basis even if only one of the two possible isomers is available. For example, for 4-methyl-*cis*-2-decalone, $W_{h/2}$ = 0.84 Hz, and for 4-methyl-*trans*-2-decalone, $W_{h/2}$ = 1.36 Hz. In the case of compound **13**, $W_{h/2} \simeq$ 0.80 Hz, a value which indicates cis ring fusion.

For compounds **12** and **15** a chemical proof was necessary in order to make a definitive stereochemical assignment. Compound **15** was converted to the terminal acetylene **18** by silyl cleavage with $Et_4N^+F^-$. Acetylene **18** was subsequently reduced to **19** by 5% Pd/C and H_2 (reaction 8). Compound **19** was found to be identical by



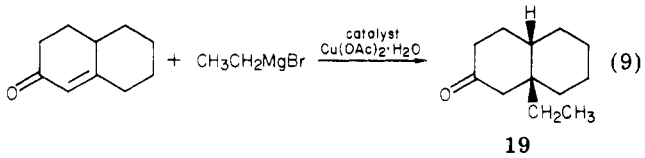
15 18



(8)

19

^{1}H and ^{13}C NMR and IR spectroscopy and gas chromatographic analysis (coinjection on two columns) with 9-ethyl-*cis*-2-decalone, prepared by the copper acetate catalyzed addition of ethyl Grignard reagent to $\Delta^{1,9}$-octalone, a sequence which has been shown to afford cis ring fusion (reaction 9).[16,20]



(9)

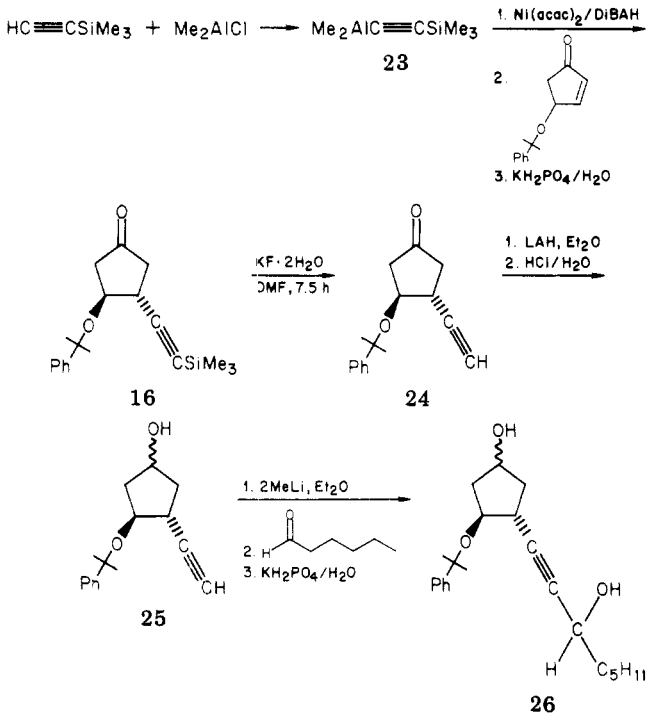
19

A final comment on the results shown in Table I involves the low yield obtained for direct acetylide addition to α,β enones via dimethylaluminum acetylide[21] (compound **11**). The conjugate adduct **11** is destroyed over a relatively short period of time in the presence of the catalytically active nickel species due to side reactions involving the product, a terminal acetylene. This result is not surprising since Ni(acac)$_2$ is known to catalyze oligomerization of monosubstituted alkynes.[22] This difficulty is easily overcome by the conversion of **10** (obtained in good yield) to the terminal acetylene through cleavage with KF.[15]

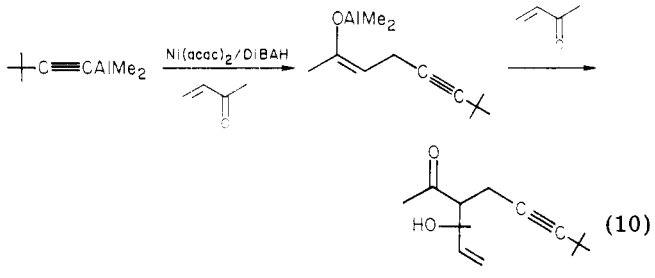
When reaction conditions were optimized for compound **14**, it was found that the highest yields of conjugate adduct were obtained when an excess of dialkylaluminum acetylide is employed. For example, using 0.22 equiv of Ni(acac)$_2$, 0.20 equiv of DiBAH, 2.2 equiv of dimethylaluminum *tert*-butylacetylide, and 1 equiv of 4-(cumyloxy)-2-cyclopentenone gave compound **14** in 85% isolated yield. Most of the unused acetylide in each case was converted on workup back to the starting acetylene and was recovered by liquid chromatography. It is important to employ an excess of aluminum acetylide because the initial product of conjugate addition is an aluminum enolate which can react with additional unsaturated ketone to give the aldol adduct. When an excess of aluminum acetylide is used, the unsaturated ketone in the presence of the nickel catalyst reacts with it rather than with the aluminum enolate. If less aluminum acetylide is employed,

(15) Corey, E. J.; Fleet, G. W. J.; Kato, M. *Tetrahedron Lett.* **1973**, 3963.
(16) Church, R. F.; Ireland, R. B.; Shredar, D. R. *J. Org. Chem.* **1962**, *27*, 707. Boatman, S.; Harris, T. M.; Hauser, C. R. *J. Am. Chem. Soc.* **1965**, *87*, 82.
(17) Williamson, K. L.; Howell, T.; Spencer, T. A. *J. Am. Chem. Soc.* **1966**, *88*, 325. Robinson, M. J. T. *Tetrahedron Lett.* **1965**, 1685.
(18) Pappo, R., private communication.
(19) Posner, G. H. *Org. React.* **1972**, *19*, 1.
(20) Marshall, J. A.; Ruden, R. A. *J. Org. Chem.* **1972**, *37*, 659.
(21) Murray, T. F.; Varma, V.; Norton, J. R. *J. Chem. Soc., Chem. Commun.* **1976**, 907.
(22) Jolly, P. W.; Wilke, G. "The Organic Chemistry of Nickel"; Academic Press: New York, 1974; Vol. II, p 284.

Scheme I



the desired conjugate adduct and the aldol condensation product are observed. For example (reaction 10), it was

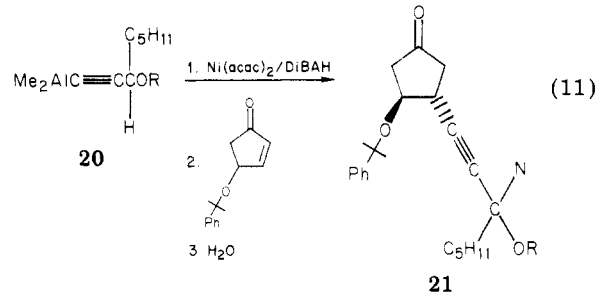


possible to isolate, in addition to the desired conjugate adduct (40% yield), the compound formed by aldol condensation of the aluminum enolate derived from conjugate addition to methyl vinyl ketone with another equivalent of methyl vinyl ketone.

A study of solvent effects on the conjugate addition reaction revealed that Lewis basic solvents such as THF are not effectively employed. However, it was also found that weak electron-donor capacity in the solvent, perhaps to break up aluminum dimers, was desirable; mixtures of hydrocarbons and ether resulted in slightly lower yields than 100% ether. For example, for the production of compound **14**, with all other conditions identical, the yield in THF was a few percent, in ether 85%, and in ether/hexane (50:50) 71%. Adding oxygen functionality to the unsaturated ketone also slows down the rate of conjugate addition. Cyclohexenone and cyclopentenone react more rapidly (usually within 15–30 min) than does 4-(cumyloxy)-2-cyclopentenone, for which optimal yields are obtained after 1.5 h.

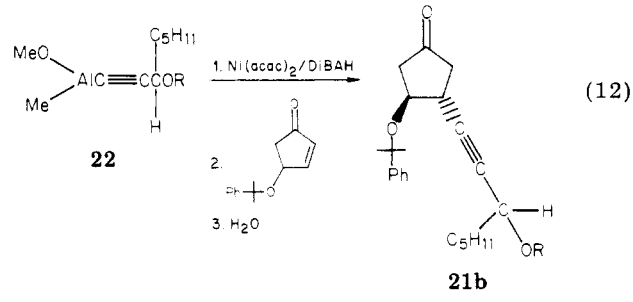
A synthetic application in which the conjugate addition of an alkynyl group would be of direct use may be found in the area of 13,14-dehydroprostaglandin chemistry. Although Pappo et al.[4,5] have conjugately added alkynyl groups to prostaglandin substrates via alkylaluminum acetylides (reactions 2 and 3), their synthesis is critically dependent upon the presence of a hydroxyl group which directs the alane to add cis to itself. Such a method is useful only for producing 11-epiprostaglandins but *not* for synthesizing the natural forms. The nickel-catalyzed conjugate addition, on the other hand, has been shown to give the desired trans stereochemistry of these groups (see Table I, compounds **14** and **16**). It was therefore of interest to determine whether the β chain of a 13,14-dehydroprostaglandin could be added directly via the nickel-catalyzed conjugate addition of an alkynylalane.

Attempts to perform the reaction (reaction 11) resulted in poor yields regardless of the hydroxyl protecting group.



R = (a) $SiMe_3$, (b) $SiMe_2$-*t*-Bu, (c) $SiEt_3$, (d) CPh_3, (e) CH_3CO, (f) $AlMe_2$

The best yield obtained with a dimethylaluminum acetylide (7%) occurred for R = $SiMe_2$-*t*-Bu. Use of modified organoalane **22** gave **21b** in 20% yield (reaction 12). In each case examined, some polymer formation was noted.



R = $Si(CH_3)_2C(CH_3)_3$

An alternate strategy for adding an alkynyl prostaglandin chain to (cumyloxy)cyclopentenone was attempted and is shown in Scheme I. The starting (trimethylsilyl)acetylene, **23**, is easily available from NaC≡CH and Me_2SiCl.[23] Conjugate adduct **16** was obtained in 55% yield under standard reaction conditions. Silyl cleavage[15] and LAH reduction proceeded in excellent yields (94 and 96%, respectively). The conversion of **25** to **26** involved the formation of a dilithium salt of **25**, which condensed with hexanal at the position of the alkynyl anion (this gave a mixture of diastereomers in 52% yield); the overall yield of **26** by this route was 26%.

Conclusions

The nickel-catalyzed conjugate addition of alkynyl units from dialkylaluminum acetylides to α,β enones is a unique addition to the repertoire of reactions available to the organic chemist. It is the only sequence known which allows this transformation for ordinary *S*-trans enones and often proceeds in high yield. In the cases investigated, the reaction was found to proceed with high stereospecificity. Moreover, only 1,4-addition was observed and this only of the alkynyl unit. As such, the reaction shown in reaction 6 should be broadly applicable in organic synthesis.

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Experimental Section

General Methods. All experiments were performed under an atmosphere of nitrogen or argon from which oxygen was removed by passing through a bed of BTS catalyst in reduced form (previously heated under a CO stream) and from which water was removed by passing it through a column of Matheson size 4A molecular sieves. The atmosphere was introduced by repeated evacuation and addition of gas to thoroughly dried glassware. Liquid transfers were performed by syringe, and solid transfers were performed under a stream of inert gas or in a drybox. All ether and hydrocarbon solvents were distilled, just prior to use, under argon or nitrogen from sodium/benzophenone ketyl. Approximately 5% tetraglyme was added to hydrocarbon solvents to ensure the solubility of the ketyl. All other solvents were distilled under argon or nitrogen from the proper drying agent (calcium hydride or lithium aluminum hydride). Commercially obtained organic compounds were dried by the appropriate method and, if liquid, distilled under argon or nitrogen directly prior to use.

Infrared (IR) spectra were obtained with either a Perkin-Elmer 237B or a Perkin-Elmer 283 spectrophotometer. Nuclear magnetic resonance (NMR) spectra were taken on a Varian A-60A spectrometer and are reported downfield from tetramethylsilane (Me_4Si) in units of δ in the order: multiplicity, intensity, and identity; 100-MHz ^1H and ^{13}C NMR spectra were obtained with a Varian XL-100 spectrometer equipped with a pulsed Fourier transform system. Mass spectra were recorded on an AEI MS-9.

Analytical thin-layer chromatography (TLC) was performed on Whatman K5 silica strips and preparative TLC on Whatman K5 20 × 20 cm plates. Preparative liquid chromatography was performed by using a Waters Associates refractive index detector, Model R403, and a Fluids Metering, Inc., solvent delivery system. Samples were run through two 310-mm EM Laboratories silica gel columns (25 mm i.d.; 28 mm o.d.) with varying percentages of hexane and ethyl acetate.

Dialkylaluminum chlorides and diisobutylaluminum hydride were obtained either neat or in solution from Texas Alkyls. *n*-Butyllithium was obtained as a solution in hexane from Aldrich.

Bis(2,4-pentanedionato)nickel, ($Ni(acac)_2$), was obtained from Alfa Products as the dihydrate. This was purified by dissolution in ether, filtration to remove impurities, removal of solvent, and thorough drying in vacuo at 100 °C.

All reactions were performed at room temperature unless otherwise stated. Literature references following spectral data indicate reported spectra of the compound in question.

Nickel-Catalyzed Conjugate Addition of Dimethylneohexynylaluminum with 4-(Cumyloxy)-2-cyclopentenone. To 0.09 g (0.36 mmol) of $Ni(acac)_2$ in 15 mL of ether at 0 °C was added 0.60 mL (0.32 mmol) of a 0.53 M solution of DiBAH in toluene. Then 8 mL (3.6 mmol) of a 0.45 M solution of dimethylneohexynylaluminum in ether, prepared by the method of Fried et al.,[24] was added to the reaction mixture. The temperature of the reaction mixture was lowered to −5 °C, and 0.36 g (1.65 mmol) of 4-(cumyloxy)-2-cyclopentenone in 10 mL of ether was added dropwise over 15 min to the reaction mixture. 4-(Cumyloxy)-2-cyclopentenone was prepared by the method of Stork and Isobe[25] and gave the following appropriate spectra: IR (neat) 1715 cm^{-1} (CO); ^1H NMR (CCl_4) δ 1.52 (s, 6), 2.25 (m, 2), 4.33 (m, 1), 5.97 (dd, 1, J = 5 Hz), 7.17 (m, 1), 7.33 (5, m). The reaction mixture was allowed to stir at −5 °C for 1.5 h and was hydrolyzed with saturated KH_2PO_4. Enough 10% aqueous H_2SO_4 was added to dissolve the Al salts. The organic layer was separated, extracted with ether, washed with saturated aqueous $NaHCO_3$ and saturated aqueous NaCl, dried with Na_2SO_4, filtered, and rotary evaporated. The major product, present in 85% yield (0.42 g), was separated by liquid chromatography (20% ethyl acetate, 80% hexane) and was found to be *trans*-3-(3,3-dimethyl-1-butynyl)-4-(cumyloxy)-cyclopentanone (**14**): IR (CCl_4) 1750 cm^{-1} (CO); Raman ν(C≡C) 2170 cm^{-1}; ^1H NMR (CCl_4) δ 1.05 (s, 9), 1.47 (s, 3), 1.53 (s, 3), 1.90–2.40 (m, 3), 2.80 (m, 2), 3.85 ("q", 1, CH–O, J = 5.2 Hz), 7.20 (m, 5); mol wt calcd 298.193 269, found 298.192 287. Also collected by liquid chromatography was 2,2,7,7-tetramethyl-3,5-octadiyne:[26] ^1H NMR (CCl_4) δ 1.12 (s, 18, *t*-Bu); mass spectrum, *m/e* (relative intensity) 162 (0.54, $M^{+\cdot}$), 32 (1.00), 43 (0.52), 41 (0.55), 119 (0.39). Anal. ($C_{12}H_{18}$) C, H.

Preparation of Protected 1-Octyn-3-ols. (A) 3-(Trimethylsiloxy)-1-octyne. To 5.93 g (47 mmol) of 1-octyn-3-ol in 60 mL of toluene was added 6.6 mL (47 mmol) of triethylamine. Then 6 mL (47 mmol) of trimethylsilyl chloride was added dropwise to the reaction mixture, which evolved heat. It was allowed to stir for 3 h and filtered, and the product, 3-(trimethylsiloxy)-1-octyne, was distilled at 63–64 °C (4 mm): IR (neat) 2100 (C≡C), 3120 cm^{-1} (≡CH); ^1H NMR (CCl_4) δ 0.12 (s, 9), 0.90 ("t", 3), 1.08–1.83 (m, 8), 2.25 (d, 1, ≡CH, J = 2 Hz), 4.28 (m, 1, $HCOSiMe_3$).

(B) 3-(*tert*-Butyldimethylsiloxy)-1-octyne.[27] To 5.39 g (42.8 mmol) of 1-octyn-3-ol in 45 mL of DMF were added 12 g (171.2 mmol) of imidazole and 9.6 g of (64.2 mmol) of *t*-$BuMe_2SiCl$. The reaction mixture was heated at 40 °C overnight, extracted with ether, washed with saturated aqueous $NaHCO_3$ and saturated aqueous NaCl, and rotary evaporated. The product, 3-(*tert*-butyldimethylsiloxy)-1-octyne, was distilled at 65.5 °C (0.15 mm): IR (neat) 2120 (C≡C), 3315 cm^{-1} (≡CH); ^1H NMR (CCl_4) δ 0.06 (s, 3), 0.10 (s, 3), 0.87 (s, 9), 0.90 (m, 3), 1.05–1.77 (m, 8), 2.55 (d, 1, ≡CH, J = 2 Hz), 4.27 (m, 1, HCOSi).

(C) 3-(Triethylsilyloxy)-1-octyne. To 2.92 g (23.1 mmol) of 1-octyn-3-ol in 20 mL of DMF were added 6.21 g (91.2 mmol) of imidazole and 4.6 mL (27 mmol) of triethylsilyl chloride (dropwise). The reaction mixture was heated at 40 °C overnight, extracted with ether, washed with water until it was acidified, washed with saturated aqueous $NaHCO_3$ and saturated aqueous NaCl, dried with Na_2SO_4, filtered, and rotary evaporated. The product, 3-(triethylsilyloxy)-1-octyne, was distilled at 62 °C (0.15 mm): IR (neat) 2110 (C≡C), 3310 cm^{-1} (≡CH); ^1H NMR (CCl_4) δ 0.67 (m, 6), 0.73–1.13 (m, 15), 1.13–1.83 (m, 8), 2.22 (d, 1, ≡CH, J = 2 Hz), 4.28 (m, 1).

(D) 3-(Triphenylmethyloxy)-1-octyne.[28] To 12.42 g (44.6 mmol) of Ph_3CCl in 30 mL of pyridine was added 5.70 g (45.1 mmol) of 1-octyn-3-ol. The reaction mixture was allowed to reflux overnight and was hydrolyzed by being poured into 200 mL of ice and water. It was extracted with ether, washed with saturated aqueous $NaHCO_3$ and saturated aqueous NaCl, dried with Na_2SO_4, filtered, and rotary evaporated. The residue was dissolved in acetone and crystallized in a freezer. The product, 3-(trityloxy)-1-octyne, was recrystallized from acetone/methanol (2:3): IR (CCl_4) 3315 cm^{-1} (≡CH); ^1H NMR (CCl_4) δ 0.83 (m, 3), 1.00–1.55 (m, 8), 1.98 (d, 1, ≡CH, J = 2 Hz), 3.98 (m, 1), 7.08–7.65 (m, 15).

(E) 3-Acetoxy-1-octyne. A solution of 5.6 mL (60 mmol) of acetic anhydride in 9.7 mL of pyridine (120 mmol) was cooled to 0 °C. To this was added 3.75 g (29.7 mmol) of 1-octyn-3-ol dropwise. The reaction mixture was allowed to stir overnight, hydrolyzed by being poured into 100 mL of ice and water, extracted with ether, rotary evaporated, and distilled: IR (neat) 1740 (C=O), 2120 (C≡C), 3300 cm^{-1} (≡CH); ^1H NMR (CCl_4) δ 0.90 (m, 3), 1.07–1.90 (m, 8), 2.00 (s, 3), 2.32 (d, 1, ≡CH, J = 2 Hz), 5.28 (tt, 1, HCOAc, J = 6 Hz, 2).

Nickel-Catalyzed Conjugate Addition of Dimethyl[3-(trimethylsiloxy)-1-octynyl]aluminum (20a) with 4-(Cumyloxy)-2-cyclopentenone. To 32.8 mmol of 3-(trimethylsiloxy)-1-octyne in 8 mL of toluene at −35 °C was added dropwise over 0.5 h 20.75 mL (32.8 mmol) of a 1.58 M solution of *n*-BuLi in hexane. The reaction mixture was allowed to stir for 10 min before the addition of 26.5 mL (31.8 mmol) of a 1.20 M solution of Me_2AlCl in toluene was added. The reaction mixture was allowed to stir at 0 °C for 2 h, during which time it became yellowish and a white solid (presumably LiCl) precipitated. The solution was calculated to be 0.49 M in dimethyl[3-(trimethylsiloxy)-1-octynyl]aluminum (**20a**).

To 0.11 g (0.43 mmol) of $Ni(acac)_2$ in 5 mL of ether at 0 °C was added 0.80 mL (0.43 mmol) of a 0.53 M solution of DiBAH in toluene. The reaction mixture was cooled to −5 °C, and 12 mL (5.88 mmol) of the above 0.79 M solution of **20a** was added. Then

(24) Fried, J.; Lin, C. H.; Sih, J. C.; Dalven, P.; Cooper, G. F. *J. Am. Chem. Soc.* **1972**, *94*, 4342, 4343.
(25) Stork, G.; Isobe, M. *J. Am. Chem. Soc.* **1975**, *97*, 6260.
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(28) Blickenstaff, R. T. *J. Am. Chem. Soc.* **1960**, *82*, 3673.

a solution of 0.41 g (1.90 mmol) of 4-(cumyloxy)-2-cyclopentenone in 10 mL of ether was added dropwise to the reaction mixture over 15 min. The reaction mixture was allowed to stir at −5 °C for 2.5 h, hydrolyzed for 45 min with dilute aqueous KH_2PO_4, extracted with ether, washed with saturated aqueous $NaHCO_3$ and saturated aqueous NaCl, dried with Na_2SO_4, filtered, and rotary evaporated. The residue was separated into three fractions by liquid chromatography (20% ethyl acetate, 80% hexane). NMR analysis of these fractions indicated that the major component was 3-(trimethylsiloxy)-1-octyne. Also present were compounds whose NMR spectra suggested that they were polymerized 3-(trimethylsiloxy)-1-octyne and polymerized 4-(cumyloxy)-2-cyclopentenone. None of the expected conjugate adduct **21a** was found to be present.

Nickel-Catalyzed Conjugate Addition Reaction of $Me_2AlC{\equiv}CCH(OAlMe_2)C_5H_{11}$ (20f) with 4-(Cumyloxy)-2-cyclopentenone. To 0.39 g (3.11 mmol) of 1-octyn-3-ol in 8 mL of toluene at −35 °C was added 3.91 mL (6.07 mmol) of a 1.58 M solution of *n*-BuLi in hexane dropwise. The reaction mixture turned yellow and became viscous, whereupon 10 mL of ether was added to dissolve the slurry. Then 1.09 g (6.17 mmol) of diisobutylaluminum chloride in 10 mL of toluene was added to the reaction mixture. The reaction mixture was allowed to stir at 0 °C for 2.5 h, during which time a white solid (LiCl) precipitated out of the pale yellow solution of $Me_2AlC{\equiv}CCH(OAlMe_2)C_5H_{11}$ (**20f**). The solid was removed by filtration.

To 0.10 g (0.40 mmol) of $Ni(acac)_2$ in 10 mL of ether at 0 °C was added 0.65 mL (0.35 mmol) of a 0.5 M solution of DiBAH in toluene. The temperature was lowered to −5 °C, and the solution of $Me_2AlC{\equiv}CCH(OAlMe_2)C_5H_{11}$ (**20f**) was added. Then a solution of 0.33 g (1.54 mmol) of 4-(cumyloxy)-2-cyclopentenone in 10 mL of ether was added dropwise to the reaction mixture over 10 min. The reaction mixture was allowed to stir between −5 and 0 °C for 2 h and was worked up in the usual fashion. Six fractions were separated by liquid chromatography (20% ethyl acetate, 80% hexane), but only the last two of these, considered likely candidates for the conjugate adduct **21f**, were analyzed. The fifth and largest fraction consisted of 1-octyn-3-ol. The sixth fraction was thought to be polymerized 4-(cumyloxy)-2-cyclopentenone on the basis of its NMR and IR spectra. None of the expected conjugate adduct **21f** was found.

Nickel-Catalyzed Conjugate Addition of Dimethyl[3-(*tert*-butyldimethylsiloxy)-1-octynyl]aluminum (20b) with 4-(Cumyloxy)-2-cyclopentenone. To 0.64 g (2.64 mmol) of 3-(*tert*-butyldimethylsiloxy)-1-octyne in 5 mL of toluene at −35 °C was added 1.67 mL (2.64 mmol) of a 1.58 M solution of *n*-BuLi in hexane. After 10 min, 0.25 g (2.65 mmol) of dimethylaluminum chloride in 10 mL of toluene was added. The reaction mixture was allowed to stir at 0 °C for 2 h.

To 0.08 g (0.30 mmol) of $Ni(acac)_2$ in 15 mL of ether at 0 °C was added 0.56 mL (0.30) mmol) of a 0.53 M solution of DiBAH in toluene. To this was added the above solution of dimethyl-[3-(*tert*-butyldimethylsiloxy)-1-octynyl]aluminum (**20b**). Then 0.37 g (1.69 mmol) of 4-(cumyloxy)-2-cyclopentenone in 20 mL of ether was added dropwise to the reaction mixture between −5 and 0 °C over 1.25 h. The reaction mixture was allowed to stir at this temperature for an additional 3.5 h and was worked up in the usual fashion. The residue was separated into six fractions by liquid chromatography (20% ethyl acetate, 80% hexane). NMR analyses showed the first fraction to contain 3-(*tert*-butyldimethylsiloxy)-1-octyne and polymerized acetylene and the sixth fraction to contain 4-(cumyloxy)-2-cyclopentenone. The second and third fractions appeared to contain the conjugate adduct **21b** and were recombined. These were separated into seven fractions by liquid chromatography (7% ethyl acetate, 93% hexane). The last two fractions were by far the largest and were found to have the following spectral characteristics. Fraction 6: IR (CCl_4) 1750 cm^{-1} (CO); ^1H NMR δ 0.06 (s, 3), 0.10 (s, 3), 0.90 (s, 9), 0.93 (m, 3), 1.13–1.63 (m, 8), 1.58 (s, 3), 1.64 (s, 3), 1.75–3.08 (br m, 5), 3.41–4.70 (m, 2), 7.36 (m, 5); ^{13}C NMR δ −4.44, −4.87, 14.00, 18.27, 22.58, 24.97, 25.82, 29.28, 31.40, 35.52, 38.70, 42.92, 45.78, 63.01, 75.07, 77.84, 83.60, 85.07, 125.85, 127.19, 128.09, 145.66, 214.90. Fraction 7: IR (CCl_4) 1750 cm^{-1} (CO); ^1H NMR δ 0.06 (s, 3), 0.10 (s, 3), 0.90 (s, 9), 0.93 (m, 3), 1.13–1.63 (m, 8), 1.46 (s, 3), 1.76 (s, 3), 1.75–3.08 (br m, 5), 3.41–4.70 (m, 2), 7.36 (m, 5); ^{13}C NMR δ −4.43, −4.87, 14.01, 18.26, 22.57, 24.96, 25.82, 29.27, 31.39, 35.52, 38.66, 43.09, 45.79, 62.99, 75.05, 77.83, 83.59, 85.05, 125.82, 127.18, 128.09, 145.62, 214.88. Both fractions 6 and 7 were assigned to conjugate adduct **21b**. It is possible that these may be epimeric at $C{\equiv}CCH(OSiR_3)R'$. Fraction 6 weighed 0.0193 g (3% yield), and fraction 7 weighed 0.0297 g (4% yield).

Reaction of 3-(Trityloxy)-1-octyne, *n*-Butyllithium, and Dimethylaluminum Chloride. To 0.70 g (1.91 mmol) of 3-(trityloxy)-1-octyne in 15 mL of toluene at −40 °C was slowly added 1.2 mL (1.91 mmol) of *n*-butyllithium in hexane. The reaction mixture was allowed to stir between −40 and −20 °C for 2.5 h. The 0.18 g (1.91 mmol) of dimethylaluminum chloride in 15 mL of toluene was added dropwise to the solution at −40 °C, after which the reaction mixture was allowed to stir at −20 °C for several hours. NMR analyses after the solvent was removed and the residue redissolved in benzene-d_6 showed that approximately 80% of the trityl group had been cleaved to form trityl chloride (δ 7.20, singlet) and that very little, if any, of the expected dimethyl[3-(trityloxy)-1-octynyl]aluminum was present.

Nickel-Catalyzed Conjugate Addition of Dimethyl(3-acetoxy-1-octynyl)aluminum (20e) with 4-(Cumyloxy)-2-cyclopentenone. To 0.40 g (2.36 mmol) of 3-acetoxy-1-octyne in 5 mL of toluene at −40 °C was added dropwise 1.5 mL (2.36 mmol) of a 1.58 M solution of *n*-butyllithium in hexane. The reaction mixture was allowed to stir at −40 °C for 2 h. The temperature was raised to −20 °C, and 0.22 g (2.36 mmol) of dimethylaluminum chloride in 8 mL of toluene was added dropwise to the reaction mixture, which was allowed to stir at −20 °C for a few hours, during which a white solid (LiCl) precipitated.

To 0.06 g (0.23 mmol) of $Ni(acac)_2$ in 15 mL of ether at 0 °C was added 0.4 mL (0.23 mmol) of a 0.53 M solution of DiBAH in toluene. To this was added the above solution of dimethyl-(3-acetoxy-1-octynyl)aluminum (**20e**). Into this mixture was added a solution of 0.26 g (1.21 mmol) of 4-(cumyloxy)-2-cyclopentenone in 20 mL of ether dropwise over 1 h. The reaction mixture was allowed to stir at −3 °C for 5 h and was worked up in the usual fashion. Analyses by liquid chromatography (20% ethyl acetate, 80% hexane) showed that the major organic components were unreacted 4-(cumyloxy)-2-cyclopentenone and free 1-octyn-3-ol. Also present was a small amount of a compound assigned to be the desired conjugate adduct **21e** on the basis of its spectra: IR (CCl_4) 1750 cm^{-1} (CO); ^1H NMR (CCl_4) δ 0.90 (m, 3), 1.02–1.67 (m, 8), 1.53 (br s, 6), 1.67–2.88 (m, 5), 1.97 (s, 3), 4.00 (m, 1), 5.40 (m, 1), 7.30 (m, 5). The yield of this adduct was very low.

Preparation of Methoxymethyl[3-(*tert*-butyldimethylsiloxy)-1-octynyl]aluminum (22). In a 100-mL Schlenk flask were mixed 5.39 g (42.8 mmol) of 1-octyn-3-ol, 12 g (4 equiv) of imidazole, and 9.6 g (1.5 equiv) of $ClSiMe_2$-*t*-Bu in 45 mL of dry DMF. The flask was fitted with a reflux condenser and a drying tube and was flushed with N_2 for 5 min. The reaction mixture was heated in an oil bath at 70 °C for 22 h. It was then taken up in 70 mL of water and extracted with 3 × 50 mL of ether. The combined ether portions were then washed with $NaHCO_3$ (4 × 50 mL), brine (2 × 50 mL), and water (1 × 50 mL), dried over Na_2SO_4, evaporated, and fractionally distilled in vacuo. The desired 3-(*tert*-butyldimethylsiloxy)-1-octyne was distilled at 62 °C (0.12 mm Hg): 9.08 g (87% yield); ^1H NMR (CCl_4) δ 0.2 (d, 6), 1.02 (s, 12), 1.25–1.85 (m, 8), 2.4 (d, 1), 4.45 (m, 1).

To 0.48 g of 3-(*tert*-butyldimethylsiloxy)-1-octyne, dissolved in 5 mL of toluene and cooled to −40 °C, was added 1.25 mL of 1.6 M *n*-butyllithium. This was allowed to stir and to warm to room temperature for 2 h under N_2.

Dimethylaluminum chloride (1.7 mL of a 1.20 M solution in hexane) was placed in a three-necked flask fitted with an N_2 inlet, bubbler, and dropping funnel. It was cooled to 0 °C. An equimolar amount of dry, degassed methanol (0.065 g) was dissolved in 8 mL of toluene and added dropwise over 5 min. The temperature was allowed to warm to 25 °C, and the mixture was stirred for an additional 3 h. To this was added previously prepared 3-(*tert*-butyldimethylsiloxy)-1-octynyllithium via cannula. The reaction mixture was stirred for 2 h at room temperature. The white LiCl was filtered off to give a solution of **22**.

Nickel-Catalyzed Conjugate Addition of Methoxymethyl[3-(*tert*-butyldimethylsiloxy)-1-octynyl]aluminum (22) with 4-(Cumyloxy)-2-cyclopentenone. To 0.105 g (0.4 mmol) of $Ni(acac)_2$ in 5 mL of Et_2O at 0 °C was added 0.8 mL

of a 0.5 M DiBAH solution in toluene. After 10 min, **22** was added via cannula. Then 0.438 g (2 mmol) of 4-(cumyloxy)-2-cyclopentenone dissolved in 35 mL of ether was added dropwise over 1 h. The reaction was stirred for 8 h at 0 °C and then worked up in the usual fashion. The reaction mixture was separated by medium-pressure liquid chromatography (20% EtOAc, 80% hexane) into 11 fractions. Fraction 4 contained the desired product (**21b**; 0.182 g, 0.4 mmol) in 20% overall yield.

Nickel-Catalyzed Conjugate Addition of Dimethyl[3-(triethylsiloxy)-1-octynyl]aluminum (20c) with 4-(Cumyloxy)-2-cyclopentenone. To 0.35 g (1.44 mmol) of 3-(triethylsiloxy)-1-octyne in 10 mL of hexane at −40 °C was added dropwise 0.95 mL (1.44 mmol) of a 1.52 M solution of *n*-butyllithium in hexane. The reaction mixture was allowed to stir between −40 and −20 °C for 2 h. Then 1.20 mL (1.44 mmol) of a 1.2 M solution of dimethylaluminum chloride in hexane was added dropwise at 0 °C. The reaction mixture was allowed to stir for 1.75 h and was filtered to remove LiCl.

To 0.04 g (0.16 mmol) of $Ni(acac)_2$ in 15 mL of ether at 0 °C was added 0.30 mL (0.16 mmol) of DiBAH in toluene. After 15 min the above solution of dimethyl[3-(triethylsilyloxy)-1-octynyl]aluminum (**20c**) was added. Then 0.15 g (0.71 mmol) of 4-(cumyloxy)-2-cyclopentenone in 18 mL of ether was added dropwise to the reaction mixture over 1.5 h. The reaction mixture was allowed to stir at 0 °C for 4 h and was worked up in the usual fashion. The reaction mixture was separated into five fractions by liquid chromatography (20% ethyl acetate, 80% hexane), and the second and third of these, thought to contain the desired conjugate adduct, **21c**, were recombined and further purified by liquid chromatography (7% ethyl acetate, 93% hexane). It was found that the fifth of six fractions contained the conjugate adduct **21c** in 3% yield (1.80×10^{-5} mol): IR (CCl_4) 1750 cm^{-1} (CO); ^1H NMR (CCl_4) δ 0.67 (m, 6), 1.00 (m, 12), 1.20–1.75 (m, 8), 1.63 (br s, 6), 1.79–2.92 (m, 5), 3.85–4.58 (m, 2), 7.37 (m, 5).

Nickel-Catalyzed Conjugate Addition of Dimethyl[2-(trimethylsilyl)ethynyl]aluminum (23) with 4-(Cumyloxy)-2-cyclopentenone. To 0.87 g (8.83 mmol) of (trimethylsilyl)acetylene (prepared by the method of Krüerke[23]) in 20 mL of ether at 0 °C was added 5.5 mL (8.83 mmol) of a 1.6 M solution of *n*-BuLi in hexane. The reaction mixture was allowed to stir at −40 °C for 1.5 h and was then added dropwise to an ether solution of 8.83 mmol of dimethylaluminum chloride at room temperature. The reaction mixture was allowed to stir at this temperature for 3.5 h and was then filtered to remove LiCl.

To 0.24 g (0.93 mmol) of $Ni(acac)_2$ in 15 mL of ether at −3 °C was added 1.1 mL (0.93 mmol) of a 0.85 M solution of DiBAH in toluene. The reaction mixture was allowed to stir at 0 °C for 10 min and was then cooled to −25 °C, after which the above solution of dimethyl[2-(trimethylsilyl)ethynyl]aluminum was added. Then 0.954 g (4.48 mmol) of 4-(cumyloxy)-2-cyclopentenone in 40 mL of ether was added dropwise to the reaction mixture over 2.5 h. The reaction mixture was stirred at −30 °C for another 6 h and worked up in the usual fashion. The conjugate adduct *trans*-3-[2-(trimethylsilyl)ethynyl]-4-(cumyloxy)cyclopentanone (**16**) was separated by liquid chromatography: 0.77 g (55% yield); IR (CCl_4) 1750 (CO), 2170 cm^{-1} (C≡C); ^1H NMR (CCl_4) δ 0.13 (s, 9), 1.52 (s, 3), 1.58 (s, 3), 1.83–2.50 (m, 4), 2.90 (m, 1), 3.97 ("q", 1, J = 5.5 Hz), 7.32 (m, 5).

Desilylation of *trans*-3-[2-(Trimethylsilyl)ethynyl]-4-(cumyloxy)cyclopentanone (16) To Form *trans*-3-Ethynyl-4-(cumyloxy)cyclopentanone (24).[15] To 0.30 g (0.95 mmol) of **16** in 15 mL of DMF were added several spatula tips full of $KF \cdot 2H_2O$. The reaction mixture was allowed to stir for 7.5 h and was worked up by the addition of ether and water. The ether layer was concentrated by rotary evaporation, and the residue was dissolved in hexane and washed with water to remove DMF. The hexane layer was dried with Na_2SO_4 and filtered, and the solvent was removed to yield 0.22 g (94% yield) of *trans*-3-ethynyl-4-(cumyloxy)cyclopentanone (**24**): IR (CCl_4) 1750 (CO), 3330 cm^{-1} (≡CH); ^1H NMR (CCl_4) δ 1.48 (s, 3), 1.54 (s, 3), 1.99 (d, 1), 1.78–2.60 (m, 4), 2.80 (m, 1), 3.87 ("q", 1, J = 5.3 Hz), 7.20 (m, 5).

Reduction of *trans*-3-Ethynyl-4-(cumyloxy)cyclopentanone (24) to *trans*-3-Ethynyl-4-(cumyloxy)cyclopentanol (25). To 0.68 mL (1.50 mmol) of a 2.2 M solution of lithium aluminum hydride in THF dissolved in 5 mL of ether was added dropwise a solution of 0.18 g (0.74 mmol) of **24** in 7 mL of ether. The reaction mixture was allowed to reflux for 2 h and to stir at room temperature overnight. It was hydrolyzed by the dropwise addition of 1.5 M HCl until bubbling had ceased.

The organic layer was extracted with ether, washed with saturated $NaHCO_3$ and then brine, dried over Na_2SO_4, and concentrated by rotary evaporation. Two isomeric products were obtained by medium-pressure liquid chromatographic separation in approximately equal amounts (total yield 96%). These were identified by NMR analysis[29] as follows. (1β,3α,4β)-3-(Cumyloxy)-4-ethynylcyclopentanol (**25a**, more polar isomer): ^1H NMR (CCl_4) δ 1.50 (s, 3), 1.58 (s, 3), 1.75 (br t, 4), 1.95 (d, 1), 2.23 (br s, 1), 2.55 (m, 1, CHC≡C), 3.90 (br q, 1, J = 8 Hz, $CHOCMe_2Ph$), 4.20 (br quintet, 1, J = 7 Hz, CHOH), 7.3 (m, 5). (1α,3α,4β)-3-(Cumyloxy)-4-ethynylcyclopentanol (**25b**, less polar isomer): ^1H NMR (CCl_4) δ 1.55 (s, 3), 1.63 (s, 3), 2.2–1.7 (m, 4), 1.92 (d, 1), 2.45 (br, 1), 2.92 (m, 1, CHC≡C), 3.80 (m, 1, $CHOCMe_2Ph$), 4.15 (m, 1, CHOH), 7.3 (m, 5).

3-(Cumyloxy)-4-(3-hydroxy-1-octynyl)cyclopentanol (26). To 0.141 g (0.58 mmol) of **25** (combined isomers) in 3 mL of THF at −40 °C was added 0.80 mL (1.28 mmol) of a 1.6 M solution of *n*-butyllithium in hexane. The reaction mixture was allowed to stir at −40 °C for 1.5 h. Then 0.08 g (0.84 mmol) of freshly distilled hexanal in 10 mL of THF was slowly added dropwise. The reaction mixture was stirred at −40 °C for 4 h and was then hydrolyzed with saturated aqueous KH_2PO_4. The organic layer was extracted with ether, and the ether layer was then washed with $NaHCO_3$ and brine, dried over Na_2SO_4, and concentrated. The residue was separated by medium-pressure chromatography (20% EtOAc, 80% hexanes). Two major products were obtained and identified as follows. (1β,3α,4β)-3-(Cumyloxy)-4-(3-hydroxy-1-octynyl)cyclopentanol [**26a**; as a mixture of epimers at C(3′)]: 0.046 g (0.13 mmol, 23%); ^1H NMR (CCl_4) δ 0.89 (m, 3), 1.2–1.4 (m, 8), 1.48 (s, 3), 1.54 (s, 3), 1.65–1.85 (m, 4), 2.55 (m, 1), 2.68–2.96 (m, 2, 2 OH), 3.9 (m, 1), 4.15 (m, 2), 7.35 (m, 5); IR (CCl_4) ν(OH) 3628 (s), 3580–3140 (br), 3030, 3060, 3090 (CH, aromatic), 2230 cm^{-1} (C≡C). (1α,3α,4β)-3-(Cumyloxy)-4-(3-hydroxy-1-octynyl)cyclopentanol [**26b**; as a mixture of epimers at C(3′)]: 0.053 g (0.15 mmol, 26%); ^1H NMR (CCl_4) δ 0.89 (m, 3), 1.15–2.24 (m, 14), 1.55 (s, 3), 1.60 (s, 3), 2.90 (m, 1), 3.7 (m, 1), 4.15 (m, 2), 7.35 (m, 5); IR (CCl_4) ν(OH) 3628 (s), 3590–3200 (br), ν(C≡C) 2230; mass spectrum, peak match for (M − 18) at m/e 326.2232 (theory for $C_{22}H_{30}O_2$, m/e 326.2246).

Copper-Catalyzed Conjugate Addition of Ethylmagnesium Bromide to 4-(Cumyloxy)-2-cyclopentenone.[16] To 8 mL (7.28 mmol) of a 0.91 M ethereal solution of ethylmagnesium bromide in 5 mL of THF were added 0.08 g of $Cu(OAc)_2 \cdot H_2O$ catalyst and 0.73 g (3.36 mmol) of 4-(cumyloxy)-2-cyclopentenone in 10 mL of THF. The reaction mixture was allowed to reflux overnight, after which the solvent was removed by evaporation. The residue was dissolved in pentane and poured into ice-cold, saturated, aqueous NH_4Cl, and then 25 mL of 12 M aqueous H_2SO_4 was added. The layers were separated, and the aqueous phase was washed with pentane. The organic layers were combined, dried with Na_2SO_4, filtered, and rotary evaporated. The major product was collected by liquid chromatography (20% ethyl acetate, 80% hexane) and was found to be *trans*-3-ethyl-4-(cumyloxy)cyclopentanone (**17**): IR (neat) 1745 cm^{-1} (CO); ^1H NMR (CCl_4) δ 0.91 (t, 3, J = 6 Hz), 1.11–1.46 (m, 3), 1.56 (s, 6), 1.89–2.46 (m, 4), 3.63 ("q", 1, J = 5.6 Hz), 7.28 (m, 5).

Copper-Catalyzed Conjugate Addition of Ethylmagnesium Bromide and $\Delta^{1,9}$-Octalone. To 3.09 g (127.1 mmol) of Mg turnings in 15 mL of ether was added dropwise 4.70 mL (63 mmol) of ethyl bromide (distilled from CaH_2) in 5 mL of ether. The reaction mixture was diluted with 43 mL of ether after several hours of being stirred and was found by titration with *sec*-BuOH to be 0.91 M in ethylmagnesium bromide. To 2.20 mL (2.00 mmol) of this solution in 10 mL of THF was added 0.02 g of $Cu(OAc)_2 \cdot H_2O$ catalyst. This was followed by the dropwise addition of 0.12 g (0.83 mmol) of $\Delta^{1,9}$-octalone in 10 mL of THF. The reaction mixture was allowed to reflux overnight, the THF was removed by evaporation, and the residue was taken up in pentane.

(29) By analogy with data reported for methylcyclopentanediol derivatives: de Clercq, P.; Samson, M.; Tavernier, D.; van Haver, D.; Vandewalle, M. *J. Org. Chem.* **1977**, *42*, 3140.

The pentane solution was poured into ice-cold, saturated, aqueous NH_4Cl, after which 25 mL of 12 M aqueous H_2SO_4 was added. The layers were separated, and the aqueous layer was washed with pentane. The organic layers were combined, dried with Na_2SO_4, and rotary evaporated. The major product, 9-ethyl-*cis*-2-decalone (**19**),[20] was collected by thin-layer chromatography (hexane): IR (CCl_4) 1715 cm^{-1} (C=O); ^1H NMR (CCl_4) δ 0.79 (t, 3, J = 7 Hz), 1.03–2.63 (m, 17); ^{13}C NMR ($CDCl_3$) δ 6.57, 21.55, 24.51, 26.76, 27.63, 31.51, 32.93, 37.37, 37.60, 40.66, 46.80, 212.64.

Desilylation of 9-[(Trimethylsilyl)ethynyl]-*cis*-2-decalone To Form 9-Ethynyl-*cis*-2-decalone (18). To 0.44 g (1.80 mmol) of 9-[(trimethylsilyl)ethynyl]-*cis*-2-decalone in 12 mL of DMF were added several spatula tips full of $(CH_3CH_2)_4NF$. The reaction mixture was allowed to stir overnight and was worked up by the addition of hexane and water. The hexane layer was washed with water and rotary evaporated to give 0.25 g (80% yield) of 9-ethynyl-*cis*-2-decalone (**18**): IR (CCl_4) 2110 (C≡C), 3310 cm^{-1} (≡CH); ^1H NMR (CCl_4) 1.24–2.51 (m, 15), 2.13 (s, 1, ≡CH); mol wt calcd 176.120 109, found 176.117 565.

Reduction of 9-Ethynyl-*cis*-2-decalone (18) to 9-Ethyl-*cis*-2-decalone (19). To a small amount of 5% Pd on charcoal in 10 mL of anhydrous methanol was added 0.14 g (0.82 mmol) of **18** in 5 mL of methanol. The apparatus was filled with H_2 and gas uptake was measured by means of a buret. After 6.5 h the reaction mixture was filtered to remove the Pd/C and rotary evaporated to give a quantitative yield of 9-ethyl-*cis*-2-decalone (**19**):[20] IR (CCl_4) 1715 cm^{-1} (CO); ^1H NMR (CCl_4) δ 0.79 (t, 3, J = 7 Hz), 1.03–2.63 (m, 17); ^{13}C NMR ($CDCl_3$) δ 6.59, 21.57, 24.52, 26.76, 27.63, 31.54, 32.94, 37.37, 37.60, 40.69, 46.81, 212.63.

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Registry No. **7**, 66529-94-0; **8**, 66529-95-1; **9**, 66529-96-2; **10**, 66529-97-3; **11**, 54125-18-7; **12**, 66529-98-4; **13**, 66529-99-5; **14**, 66530-00-5; **15**, 66530-01-6; **16**, 66530-02-7; **17**, 73838-35-4; **18**, 73838-36-5; **19**, 32980-04-4; **20a**, 73838-37-6; **20b**, 71120-86-0; **20c**, 73838-38-7; **20e**, 73838-39-8; **20f**, 73838-40-1; **21b**, 73838-41-2; **21c**, 73838-42-3; **21e**, 73838-43-4; **22**, 73838-44-5; **23**, 66530-05-0; **24**, 73838-45-6; **25a**, 73838-46-7; **25b**, 73890-06-9; **26a** (epimer 1), 73838-47-8; **26b** (epimer 1), 73890-08-1; 3,3-dimethyl-1-butyne, 917-92-0; 1-hexyne, 693-02-7; ethynyltrimethylsilane, 1066-54-2; ethyne, 74-86-2; 2-cyclopenten-1-one, 930-30-3; 2-cyclohexen-1-one, 930-68-7; 4,4a,5,6,7,8-hexahydro-2(3*H*)-naphthalenone, 1196-55-0; 4,4a,5,6,7,8-hexahydro-4a-methyl-2(3*H*)-naphthalenone, 826-56-2; 4-(cumyloxy)-2-cyclopenten-1-one, 65457-77-4; bis(2,4-pentanedionato-*O*,*O'*)nickel, 3264-82-2; diisobutylaluminum hydroxide, 1191-15-7; dimethyl(neohexynyl)aluminum, 66530-03-8; 3-(trimethylsiloxy)-1-octyne, 73061-39-9; 1-octyn-3-ol, 818-72-4; 3-(*tert*-butyldimethylsiloxy)-1-octyne, 60134-93-2; 3-((triethylsilyl)oxy)-1-octyne, 73838-48-9; 3-((triphenylmethyl)oxy)-1-octyne, 52418-74-3; triphenylmethyl chloride, 76-83-5; 3-acetoxy-1-octyne, 54315-33-2; diisobutylaluminum chloride, 1179-25-5; dimethylaluminum chloride, 1184-58-3; 3-(*tert*-butyldimethylsiloxy)-1-octynyllithium, 60134-82-9; **26a** (epimer 2), 73890-07-0; **26b** (epimer 2), 73890-09-2; hexanol, 66-25-1; 2,2,7,7-tetramethyl-3,5-octadiyne, 6130-98-9.

Anthra[1,2-*b*]pyran Antibiotics: Total Synthesis of *O*-Methylkidamycinone

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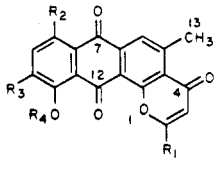
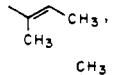
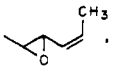
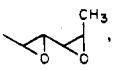
A regiospecific total synthesis of *O*-methylkidamycinone (**1d**) is described. Ethyl 2-methoxy-6-methylbenzoate (**6a**) was transformed to 7-methoxy-3-(phenylsulfonyl)-1(3*H*)-isobenzofuranone (**7c**) which was converted to an anion and condensed with methyl crotonate to afford methyl 3-methyl-1,4,8-trimethoxynaphthoate (**8a**) after methylation. The 3-methyl group of **8a** was brominated, and the introduced bromine was displaced with sodium thiophenoxide to give **8c** which was oxidized to the corresponding sulfoxide **8d**. The anion of sulfoxide **8d** was condensed with 3-penten-2-one to furnish 2-acetyl-1-hydroxy-3-methyl-8,9,10-trimethoxyanthracene (**9a**). The dilithium anion of **9a** was prepared and condensed with tiglaldehyde to afford (2′*E*,4′*E*)-2-(4′-methylhexa-2′,4′-dienoyl)-1-hydroxy-3-methyl-8,9,10-trimethoxyanthracene (**13**). Cyclization and dehydrogenation of **13** with selenium dioxide afforded (1′*E*)-5-methyl-2-(1′-methyl-1′-propenyl)-7,11,12-trimethoxy-4*H*-anthra[1,2-*b*]pyran-4-one (**15**). Oxidative cleavage of the 7,12-dimethoxy groups of **15** completed the construction of **1d**.

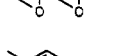
Kidamycin (**1a**),[2] pluramycin A (**1b**),[3] hedamycin (**1c**),[4] and indomycins[5] are members of a family of structurally similar anticancer antibiotics which have been isolated from various streptomyces species. Those antibiotics for which complete structures have been established have an



1a R_1 =  , R_2 = angolosamine, R_3 = N,N-dimethylvancosamine, R_4 = H

1b R_1 =  , R_2 = angolosamine, R_3 = N,N-dimethylvancosamine, R_4 = H

1c R_1 =  , R_2 = angolosamine, R_3 = N,N-dimethylvancosamine, R_4 = H

1d R_1 =  , $R_2 = R_3 = H$, $R_4 = CH_3$

anthra[1,2-*b*]pyran nucleus substituted with the amino sugars angolosamine and *N*,*N*-dimethylvancosamine at the 8- and 10-positions, respectively. The structural diversity of the antibiotics is due to the variety of unsaturated chains

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