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VICINAL ALKYNYLATION-ALKYLATION VIA A TANDEM MICHAEL ADDITION - TRANSITION METAL CATALYZED ALKYLATION REACTION

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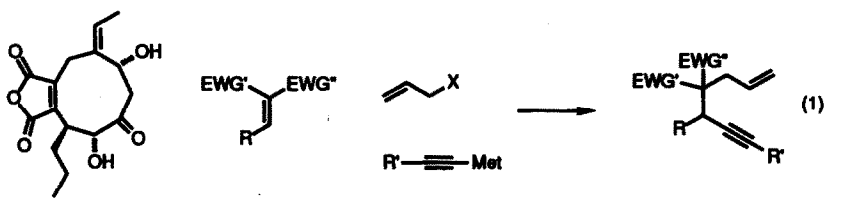
Summary: A protocol whereby addition of alkynylalanes to alkylidenemalonates is followed by palladium catalyzed allylation permits vicinal β-alkynylation α-allylation in a single operation.

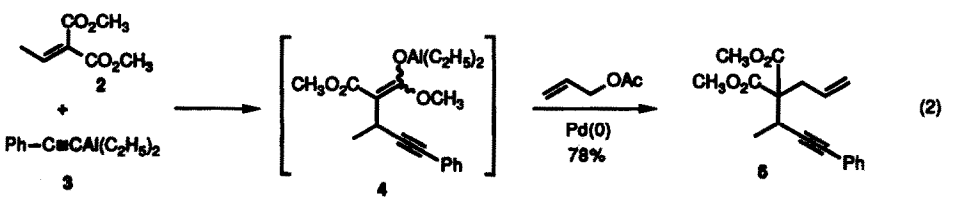
In conjunction with our interest in the synthesis of the potent nonadride herbicide cornexistin **1**,[1] we became interested in the vicinal alkylation illustrated in eq. 1. While sequential conjugate addition of alkyl and



1

alkenyl groups via organocuprate chemistry followed by alkylation is well documented,[2] such reactions initiated by conjugate addition of alkynes have normally not been successful. Conjugate additions of alkynes require alkynylaluminum[3,4] and alkynylborane[5] reagents.[6] The low reactivity of the resulting enolate makes further alkylation reactions improbable. On the other hand, the good reactivity of palladium catalyzed alkylations with highly stabilized nucleophiles[7] led us to examine the feasibility of the sequence of eq. 1 wherein the allylation is catalyzed by palladium.

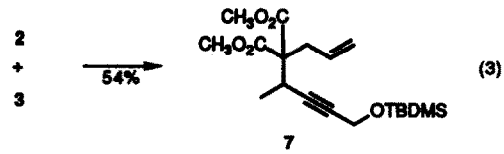
We explored dimethyl ethylidenemalonate (**2**) as a test substrate (eq. 2). Diethylphenylethynylalane (**3**), generated in normal fashion by lithiation with n-butyllithium followed by transmetalation with diethylaluminum chloride, reacted with **2** at room temperature in a 5:3 hexane-ether mixture to generate presumably the aluminum



enolate **4**. Addition of an allyl acetate and a Pd(0) complex failed to give any allylation product. On the other hand, replacement of the hexane-ether with THF followed by allyl acetate and addition of the resultant solution to

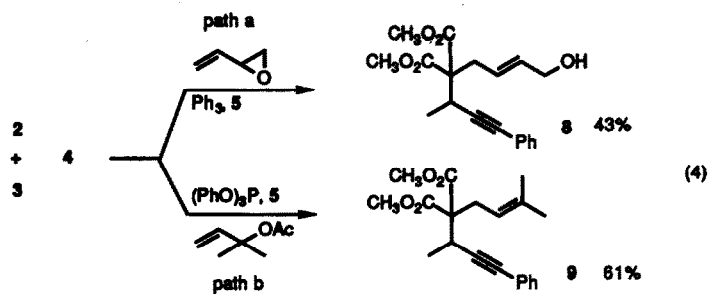
a THF solution of a Pd(0) catalyst (2 mol%) generated from $(dba)_3Pd_2 \cdot CHCl_3$ (5) and 9 mol% TTP (triphenylphosphine) gave the desired vicinal disubstituted product 6 in 78% yield after heating at reflux for 5 h.

Using the acetylide from the silyl ether of propargyl alcohol under otherwise identical conditions led to smooth reation to give the vicinal disubstituted product 7[8] (eq. 3). On the other hand, changing the allyl partner



(3)

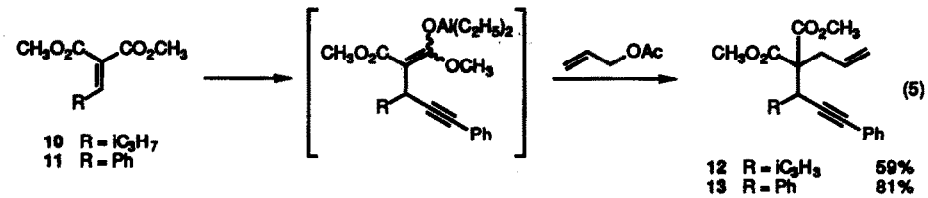
required changing the solvent and/or ligand. For example, adding butadiene monoepoxide to 4 as described above led to no alkylation. However, using DMSO instead of THF with all other factors being the same produced the desired double alkylation product 8[8] (eq. 4, path a). With 3-acetoxy-3-methyl-1-butene, both the solvent and



(4)

ligand required modification. The doubly substituted product 9[8] was produced using DMSO as solvent and triphenyl phosphite as ligand (eq. 4, path b). Interestingly, neither TPP nor triisopropyl phosphite served as ligands for this reaction.

Substituents on the alkylidenemalonate did not have much of an effect. Increasing the steric hindrance by switching from methyl to isopropyl as in 10 or introducing a conjugating substituent like phenyl as in 11 did not affect the reaction. In both cases, the original protocol generated the desired products 12[8] and 13.[8]



(5)

The requirement for as non-coordinating a solvent as possible for the addition of the alkynylalane and a more polar solvent for the allylic alkylation necessitated the change of solvent in the above procedure. A

modification of the conditions for the first stage obviated the need for this change in solvent. Forming the alane 3 in 6:1 hexane-THF still permitted the conjugate addition. Simply diluting the resultant reaction mixture with an additional 20 parts of THF then allowed the palladium catalyzed allylic alkylation to proceed. For these experiments, π-allylpalladium chloride dimer was employed as the palladium(0) source. In this way, **6** (eq. 2) and **12** (eq. 5) were obtained in 57% and 65% yields respectively.

Experimental Procedure. A solution of n-butyllithium in hexane (0.8 mL, 1.5 M, 1.2 mmol) followed after 15 min by *0.5 mL of THF and a solution of diethylalaminum chloride in hexane (0.44 mL, 2.5 M, 1.1 mmol)* was added to phenylacetylene (102 mg, 1 mmol) in 2 mL of hexane at 0°. After stirring 30 min, dimethyl ethylidenemalonate (158 mg, 1 mmol) was added and the reaction stirred 3 h at room temperature. After *sequential addition of 10 mL of THF, 150 mg (1.5 mmol) of allyl acetate, 24 mg (0.09 mmol) of TPP, and 3.7* mg ((0.0) *mmol)) of π-allyl)palladium chloride, the reaction was heated at 75-80° for 10 h, cooled, diluted with* hexane, filtered and concentrated. Chromatography of the residue (25:1 hexane-ethyl acetate) gave 171 mg (57%) of **6**.

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8. Characterization of the products:

6: ^{1}H NMR ($CDCl_3$): δ 1.4 (d, J = 7.0Hz, 3H), 2.88 (dd, J = 1.1, 7.3Hz, 2H), 3.40 (q, J = 7.0Hz, 1H), 3.76 (s, 3H), 3.79 (s, 3H), 5.05-5.25 (m, 2H), 5.82 (m, 1H), 7.25-7.45 (m, 5H). ^{13}C NMR ($CDCl_3$): δ 17.51, 31.21, 38.59, 52.28, 52.35, 61.37, 83.26, 89.73, 118.96, 123.42, 127.87, 128.19, 131.57, 132.92, 169.93, 170.28. IR (neat): 2200, 1736, 1630, 1605, 1580, 1485, 1435 cm.$^{-1}$ HRMS: Calc'd for $C_{18}H_{20}O_4$: 300.1362. Found: 300.1343.

7: ^{1}H NMR ($CDCl_3$): δ 0.11 (s, 6H), 0.90 (s, 9H), 1.29 (d, J = 7.1Hz, 3H), 2.80 (d, J = 7.2Hz, 2H), 3.20 (q, J = 6.9Hz, 1H), 3.72 (s, 3H), 3.75 (s, 3H), 4.30 (d, J = 2.1Hz, 2H), 5.10 (m, 2H), 5.8 (m, 1H). ^{13}C NMR ($CDCl_3$): δ -5.44, 17.26, 18.03, 25.60, 30.54, 38.37, 51.73, 52.09, 52.17, 61.04, 81.74, 84.68, 119.03, 133.09, 170.21, 170.60. IR (neat): 2270, 1735, 1640, 1463, 1435 cm.$^{-1}$ HRMS: Calc'd for $C_{15}H_{23}O_5$ (M^+-C_4H_9): 311.1315. Found: 311.1307.

8: ^{1}H NMR ($CDCl_3$): δ 1.38 (d, J = 6.9Hz, 3H), 1.6 (br, 1H), 2.88 (m, 2H), 3.40 (q, J = 6.9Hz, 1H), 3.76 (s, 3H), 3.78 (s, 3H), 4.08 (d, J = 4.6Hz, 2H), 5.75 (m, 2H), 7.2-7.5 (m, 5H). ^{13}C NMR ($CDCl_3$): δ 17.25, 30.98, 36.74, 52.25, 52.32, 61.34, 63.33, 83.41, 89.72, 126.84, 128.12, 128.40, 128.56, 131.74, 133.76, 170.20, 170.60. IR (neat): 3400, 2250, 1731, 1600, 1435 cm.$^{-1}$ HRMS: Calc'd for $C_{19}H_{20}O_4$ (M^+-H_2O): 312.1362. Found: 312.1349.

9: ^{1}H NMR ($CDCl_3$): δ 1.38 (d, J = 7.0Hz, 3H), 1.65 (s, 3H), 1.70 (s, 3H), 2.78 (dd, J = 7.1, 14.8Hz, 1H), 2.92 (dd, J = 7.9, 14.7Hz, 1H), 3.41 (q, J = 7.0Hz, 1H), 3.74 (s, 3H), 3.77 (s, 3H), 5.1 (m, 1H), 7.2-7.5 (m, 5H). ^{13}C NMR ($CDCl_3$): δ 17.33, 17.67, 25.89, 30.73, 32.62, 52.09, 52.16, 61.21, 83.04, 90.21, 118.20, 123.71, 127.94, 128.32, 131.75, 135.79, 170.60, 170.92. IR (neat): 1735, 1580, 1435 cm.$^{-1}$ HRMS: Calc'd for $C_{20}H_{24}O_4$: 328.1675. Found: 328.1654.

12: ^{1}H NMR ($CDCl_3$): δ 0.93 (d, J = 6.6Hz, 3H), 1.12 (d, J = 7Hz, 3H), 2.15 (m, 1H), 2.88 (dd, J = 7.5, 13Hz, 1H), 3.05 (dd, J = 7.4, 14Hz, 1H), 3.30 (d, J = 2.4Hz, 1H), 3.76 (s, 6H), 5.15 (m, 2H), 5.80 (m, 1H), 7.3-7.5 (m, 5H). ^{13}C NMR ($CDCl_3$): δ 18.64, 23.80, 28.13, 39.08, 43.04, 52.17, 52.24, 60.68, 85.62, 86.63, 119.26, 123.88, 127.89, 128.32, 131.76, 132.81, 170.47, 171.16. IR (neat): 2200, 1751, 1625, 1600, 1490, 1436 cm.$^{-1}$ HRMS: Calc'd for $C_{20}H_{24}O_4$: 328.1675. Found: 328.1674.

13: ^{1}H NMR ($CDCl_3$): δ 2.57 (dd, J = 7.3, 14.3Hz, 1H), 3.0 (dd, J = 7.1, 14.3Hz, 1H), 3.64 (s, 3H), 3.78 (s, 3H), 4.73 (s, 1H), 5.15 (m, 2H), 5.85 (m, 1H), 7.25-7.5 (m, 10H). ^{13}C NMR ($CDCl_3$): δ 38.09, 42.44, 52.00, 52.16, 63.16, 84.88, 88.32, 118.85, 123.44, 127.90, 128.14, 128.29, 128.43, 129.75, 131.71, 133.24, 136.95, 169.79, 169.94. IR (neat): 1741, 1625, 1600, 1491, 1455, 1435 cm.$^{-1}$ HRMS: Calc'd for $C_{23}H_{22}O_4$: 362.1518. Found: 362.1545.

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