from 13 in a controlled manner required a judicious choice of reaction sequence. In view of the extreme acid lability of dienol ethers, it was deemed prudent to generate the dienophile first. A standard oxidation followed by thermal elimination cleanly secured exo-methylene lactone 14.[7] Transformation of the *Z*-dienol ether entailed ester hydrolysis ensued by stereospecific anti-dehydrative decarboxylation (vide supra); the intensely UV-active tetraene 7 was thus obtained in 95% yield as a crude oil. Remarkably, attempts to purify this extremely acid-sensitive tetraene by neutral alumina chromatography (Brockmann 1 from Aldrich, hexanes/ethyl acetate, 20 °C, 1 h) resulted in the unexpected formation of the desired cycloadduct 3 in 83% yield from 14.[12] The tetracyclic lactone 3, the key, advanced intermediate in the synthesis of (±)-verrucarol by Trost and McDougal,[13] was identical by 300-MHz ^{1}H NMR, IR, and MS comparisons to authentic 3.

The formal total synthesis of (±)-verrucarol delineated above features the highly expedient production of the tetracyclic lactone 3, 17 steps in 16.6% overall yield from 2-methyl-1,3-cyclopentanedione. The efficient intramolecular Diels–Alder approach allows simultaneous and diastereoselective construction of the unique A/B rings of the trichothecene skeleton and may be applicable to the synthesis of the A-ring-oxygenated trichothecenes with a small modification. Furthermore, the serendipitously discovered room-temperature alumina-catalyzed cycloaddition should add a new dimension to Diels–Alder methodologies by potentiating the cycloaddition of thermally unstable and/or acid-labile components. Current efforts in these laboratories include probing applicability of this heretofore unprecedented[14] catalysis of the intramolecular Diels–Alder reaction by neutral alumina.

Acknowledgment. We are grateful to the National Institutes of Health (ES-02851) for the support of this work. We thank Professor B. M. Trost for the spectra of the authentic 3.

(12) Purification of the crude tetraene 7 by flash column chromatography on neutral alumina gave, in addition to the cycloadduct 3 (ca. 30% yield from 14), pure tetraene 7, which did not undergo intramolecular Diels–Alder cycloaddition upon heating to 250 °C.

(13) Trost, B. M.; McDougal, P. G. *J. Am. Chem. Soc.* **1982**, *104*, 6110; **1984**, *106*, 383.

(14) In one case neutral alumina was reported to affect the endo/exo ratio of an intermolecular Diels–Alder reaction conducted at 50 °C for 4 h. See: Parler, H.; Baumann, R. *Angew. Chem., Int. Ed. Engl.* **1981**, *20*, 1014.

(15) Yield based on recovered starting material.

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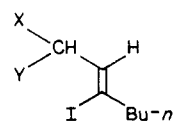
Palladium-Catalyzed Procedures for [3 + 2] Annulation via Intramolecular Alkenylpalladation and Arylpalladation[1]

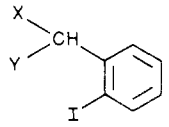
Summary: Treatment of dienolates derived from cyclohexenes activated by carbonyl groups with γ-iodoallyl electrophiles 1 and *o*-iodobenzyl electrophiles 2 followed by cyclization catalyzed by Pd complexes, e.g., $Pd(PPh_3)_4$, can produce the corresponding [3 + 2] annulated bicyclic and polycyclic derivatives.

Sir: Annulation, i.e., building a ring onto a preexisting system,[2] is an important synthetic operation. Particularly useful are those involving fusion of a new ring onto a preexisting ring in which all new ring constructing components other than those at the bridgeheads are externally introduced. There are a number of satisfactory methods for the [4 + 2] annulation[2] of this class, such as the Robinson annulation sequence and the Diels–Alder reaction.[3] The aldol cyclization and the Nazarov reaction[4] are two of the classical procedures for the [3 + 2] annulation. In addition, a fair number of procedures[5–7] for the [3 + 2] annulation have recently been developed. Despite these developments, the current scope of the [3 + 2] annulation methodology is considerably more limited than its [4 + 2] counterpart. Some desirable [3 + 2] annulation types are schematically shown (Scheme I) using cyclohexene derivatives as representative substrates.

Herein described are some examples of type I and type II annulation reactions via intramolecular carbopalladation,[8,9] which feature the use of 1 and 2 as three-carbon synthons. Experimental results are shown in eq 1–8 (Chart I).



1a: X = H, Y = Br
b: X = H, Y = I
c: X, Y = O



2a: X = H, Y = Br
b: X = H, Y = I
c: X, Y = O

Treatment of methyl 1-cyclohexenecarboxylate (3) with lithium diisopropylamide (LDA) and HMPA, followed by addition of **1a** and **1c**, gave **4** and **5**, respectively, in 70–80% yields.[10] The reaction of the lithium enolate of 3 with **2c**, followed by oxidation with CrO_3 and pyridine, provided **6**. Cyclic carbopalladation of **4–6** in the presence of 3–5 mol % of $Pd(PPh_3)_4$ and 1.5–2.0 equiv of NEt_3 in refluxing THF–MeCN (100 °C bath temperature) pro-

(1) Metal-Promoted Cyclization. 21. Part 20: O'Connor, B.; Zhang, Y.; Negishi, E.; Luo, F. T.; Cheng, J. W. *Tetrahedron Lett.* **1988**, *29*, 3903.

(2) For a review, see: Jung, M. E. *Tetrahedron* **1976**, *32*, 3.

(3) For a review, see: Oppolzer, W. *Angew. Chem., Int. Ed. Engl.* **1977**, *16*, 10.

(4) For a review, see: Santelli-Rouvier, C.; Santelli, M. *Synthesis* **1983**, 429.

(5) Noteworthy recent developments of type I [3 + 2] annulation procedures include the following: (a) Danheiser, R. L.; Carini, D. J.; Basak, A. *J. Am. Chem. Soc.* **1981**, *103*, 1604. (b) Bucheister, A.; Klemarzyk, P.; Rosenblum, M. *Organometallics* **1982**, *1*, 1679. (c) Piers, E.; Karunaratue, V. *J. Chem. Soc., Chem. Commun.* **1983**, 935. (d) Trost, B. M.; Chan, D. M. T. *J. Am. Chem. Soc.* **1983**, *105*, 2315, 2326. (e) Boger, D. L.; Brotherton, C. E. *J. Am. Chem. Soc.* **1984**, *106*, 805.

(6) For papers on type II [3 + 2] annulation, see: (a) Macdonald, T. L.; Mahalingam, S. *J. Am. Chem. Soc.* **1980**, *102*, 2113. (b) Majetich, G.; Desmond, R.; Casares, A. M. *Tetrahedron Lett.* **1983**, *24*, 1913. (c) Majetich, G.; Hull, K.; Defauw, J.; Shawe, T. *Tetrahedron Lett.* **1985**, *26*, 2755.

(7) For papers on type III [3 + 2] annulation, see: (a) Corey, E. J.; Kuwajima, I. *J. Am. Chem. Soc.* **1970**, *92*, 395. (b) Noyori, R. *Acc. Chem. Res.* **1979**, *12*, 61. (c) Stork, G.; Baine, N. H. *J. Am. Chem. Soc.* **1982**, *104*, 2321.

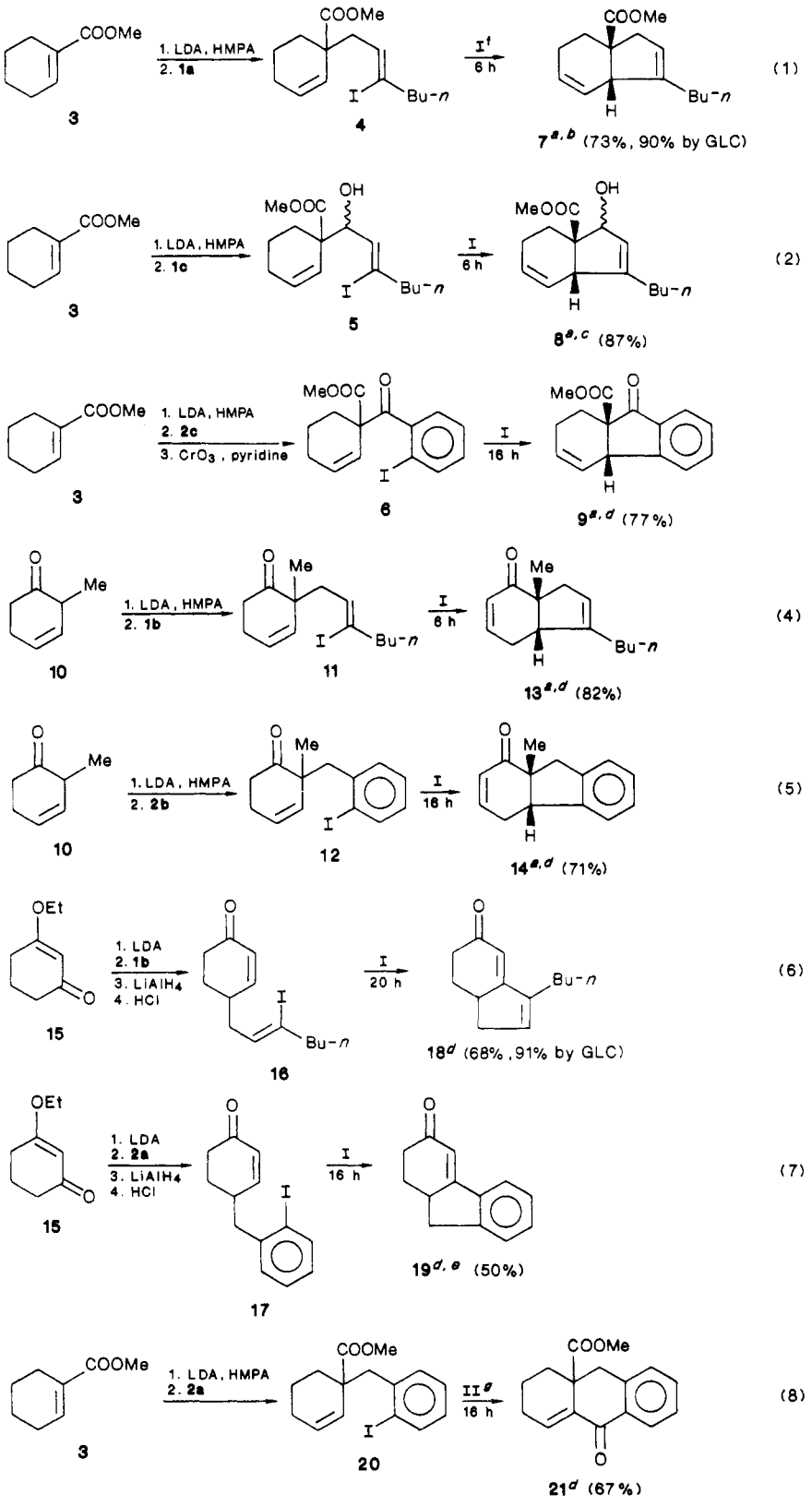
(8) For a review of the Heck-type carbopalladation–dehydropalladation reaction, including many references on the synthesis of heterocycles, see: (a) Heck, R. F. *Org. React. (N.Y.)* **1982**, *27*, 345. (b) Heck, R. F. *Palladium Reagents in Organic Syntheses*; Academic: New York, 1985.

(9) (a) Narula, C. K.; Mak, K. T.; Heck, R. F. *J. Org. Chem.* **1983**, *48*, 2792. (b) Grigg, R.; Stevenson, P.; Worakun, T. *J. Chem. Soc., Chem. Commun.* **1984**, 1073; *Tetrahedron* **1988**, *44*, 2033. (c) Tour, J. M.; Negishi, E. *J. Am. Chem. Soc.* **1985**, *107*, 8289. (d) Abelman, M. M.; Oh, T.; Overman, L. E. *J. Org. Chem.* **1987**, *52*, 4133. (e) Abelman, M. M.; Overman, L. E. *J. Am. Chem. Soc.* **1988**, *110*, 2328. (f) Negishi, E.; Zhang, Y.; O'Connor, B. *Tetrahedron Lett.* **1988**, *29*, 2915. (g) Larock, R. C.; Song, H.; Baker, B. E.; Gong, W. H. *Tetrahedron Lett.* **1988**, *29*, 2919.

(10) Herrmann, J. L.; Kieczykowski, G. R.; Schlessinger, R. H. *Tetrahedron Lett.* **1973**, 2433.

0022-3263/88/1953-5588$01.50/0

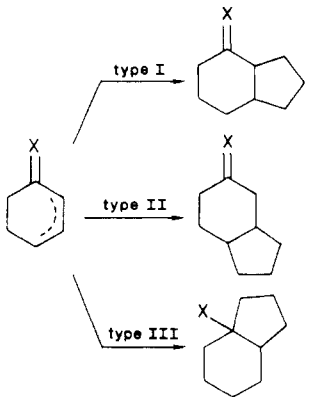
Chart I



[a] Stereoisomerically >95% pure. The stereochemical assignment is based on ^{1}H 2D NOESY NMR spectra or the measurement of ^{1}H NMR coupling constants. [b] Contains the bicyclo[4.3.0]nona-3,7-diene isomer to the extent of ca. 10%. [c] A single regioisomer but a 6:4 mixture of α-OH and β-OH stereoisomers. [d] Pure single regioisomer, >95%. [e] In addition, the double bond hydrogenated byproduct was obtained in 30% yield. [f] I: 3–5% $Pd(PPh_3)_4$, NEt_3 (1.5–2.0 equiv), THF–MeCN, 100 °C. [g] II: 5% $Pd(PPh_3)_4$, NEt_3 (1.5 equiv), CO (600 psi), THF–MeCN, 100 °C.

ceeded smoothly to give 7–9 in the indicated yields. Although 7 contains a regioisomer, tentatively identified as the 3,7-diene isomer of 7, to the extent of ca. 10%, 8 and 9 are regiochemically >95% homogeneous. The stereochemical relationship between the OH and COOMe groups of 8 is 60% trans and 40% cis. The stereochemistry of the

Scheme I[a]



[a] X = H_2, O, etc.

ring fusion is ≥98% cis as judged by inspection of their ^{1}H 2D NOESY NMR spectra and/or 1D ^{1}H-decoupled spectra as well as ^{13}C NMR spectra. For example, the ^{1}H 2D NOESY NMR spectrum of **9** clearly indicates that the proton that is β and cis to the COOMe group is also cis to the bridgehead proton and that the other β proton is trans to it.

The reaction of the lithium enolate of 3-cyclohexenone with **1b** and **2b** under mild and well-controlled conditions gave the corresponding deconjugated derivatives. Unfortunately, however, their treatment with $Pd(PPh_3)_4$–NEt_3 only induced double-bond isomerization to produce the conjugated enones which showed no sign of cyclization. The use of **10**, obtained by methylation of 3-cyclohexenone, however, cleanly produced **11** and **12** from **1b** and **2b**, respectively. As expected, their treatment with 3–5 mol % of $Pd(PPh_3)_4$ and NEt_3 (1.5–2.0 equiv) gave isomerically pure **13** and **14** in 82 and 71% yields, respectively. The stereochemical assignments are based on the same protocol as described above. Although the scope of these type I annulation procedures appears to be limited to the cases of β,γ-unsaturated carbonyl derivatives which cannot isomerize into the α,β-unsaturated derivatives, the results shown in eq 1–5 nonetheless represent efficient and selective [3 + 2] annulation procedures which appear to be of considerable synthetic utility.

To demonstrate the feasibility of type II annulation of 2-cyclohexenone derivatives, we prepared **16** and **17** by treating **15** with LDA, **1b**, and **2c**, respectively, followed by reduction with $LiAlH_4$ and deethylation with HCl. Under the Pd-catalyzed cyclization conditions, **16** was cleanly converted into **18** in 68% yield (91% by GLC), which is isomerically homogeneous. Likewise, **17** gave **19** in 50% yield. In addition to **19**, the double bond hydrogenated byproduct was also obtained in 30% yield. Similar radical cyclization procedures have recently been developed.[11] However, the C=C bond of the enone group is lost in the radical cyclization reactions.

Finally, the feasibility of achieving carbonylative [3 + 2 + 1] annulation was tested by treating **20**[12] with CO (600 psi) in the presence of 5 mol % of $Pd(PPh_3)_4$ and NEt_3 (1.5 equiv) at 100 °C. After 16 h, isomerically pure **21** was obtained in 67%. We are currently investigating the scope of this carbonylative annulation reaction.

The following procedure for the conversion of **10** into **13** is representative. 3-Cyclohexen-1-one[13] prepared by the Birch reduction of anisole was converted into **10** in 70% yield by sequential treatment with LDA (1 equiv, −78 °C, 1 h) in a 2:1 mixture by volume of THF and HMPA, CH_3I (3–5 equiv, −78 °C, 12 h), and 3 M HCl (−78 °C). Sequential treatment of **10** (5 mmol) in 10 mL of THF with LDA (5 mmol), HMPA (5 mL), and **1b** (2.10 g, 6 mmol, −78 °C, 6 h) gave a 62% yield of **11**. A mixture of **11** (0.664 g, 2 mmol), $Pd(PPh_3)_4$ (0.069 g, 0.06 mmol), NEt_3 (0.404 g, 4 mmol), and 10 mL of MeCN was refluxed for 6 h. The reaction mixture was quenched with 3 M HCl, extracted with ether, washed with aqueous $NaHCO_3$ and brine, dried over $MgSO_4$, concentrated, and flash chromatographed (silica gel, 1:10 ether–hexane) to give 0.334 g (82%) of **13**: IR (neat) 1670 (s) cm^{-1}; ^{1}H NMR ($CDCl_3$, Me_4Si) δ 0.89 (t, J = 7 Hz, 3 H), 1.24 (s, 3 H), 1.2–1.6 (m, 4 H), 1.8–2.0 (m, 2 H), 2.10 (d, J = 15 Hz, 1 H), 2.40 (dt, J = 19 and 4 Hz, 1 H), 2.58 (br d, J = 19 Hz, 1 H), 2.76 (br s, 1 H), 2.85 (d, J = 15 Hz, 1 H), 5.37 (s, 1 H), 5.99 (d, J = 10 Hz, 1 H), 6.77 (dt, J = 10 and 4 Hz, 1 H); ^{13}C NMR ($CDCl_3$) δ 13.80, 21.97, 22.40, 23.95, 28.92, 29.25, 41.12, 50.40, 53.21, 123.63, 129.68, 145.48, 145.65, 204.39; high-resolution MS calcd for $C_{14}H_{20}O$ 204.1514, found 204.1513.

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(11) Marinovic, N. N.; Ramanathan, H. *Tetrahedron Lett.* **1983**, *24*, 1871.

(12) The Pd-catalyzed cyclization reaction of **20** was recently reported as an isolated case of annulative carbocycle formation.[9d]

(13) Birch, A. J.; Bandara, B. M. R.; Chamberlain, K.; Chauncy, B.; Peter, D.; Day, A. I.; Jenkins, I. D.; Kelley, L. F.; Khor, T. *Tetrahedron, Suppl.* **1981**, 289.

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Prostaglandin Synthesis via Two-Component Coupling. Highly Efficient Synthesis of Chiral Prostaglandin Intermediates 4-Alkoxy-2-alkyl-2-cyclopenten-1-one and 4-Alkoxy-3-alkenyl-2-methylenecyclopentan-1-one

Summary: Starting with readily available (2*R*,3*S*)-1,2-epoxypent-4-en-3-ol (**5**), two chiral prostaglandin intermediates 4-alkoxy-2-alkyl-2-cyclopenten-1-one (**1**) and 4-alkoxy-3-alkenyl-2-methylenecyclopentan-1-one (**2**) are prepared in good overall yields through the common key intermediate 3,4-dialkoxy-2-methylenecyclopentan-1-one (**3**), thus making prostaglandin synthesis via two-component coupling an industrially viable process.

Sir: One of the most attractive methods for synthesis of prostaglandins (PGs) and their analogues is undoubtedly the two component coupling process via conjugate addition.[2] This process can be classified into two possible

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