addition of dihydrojasmone (final concentration of 0.6 M) to a solution of (+)-pulegone (0.16 M) in methylene chloride did not affect the rate of oxygen consumption.

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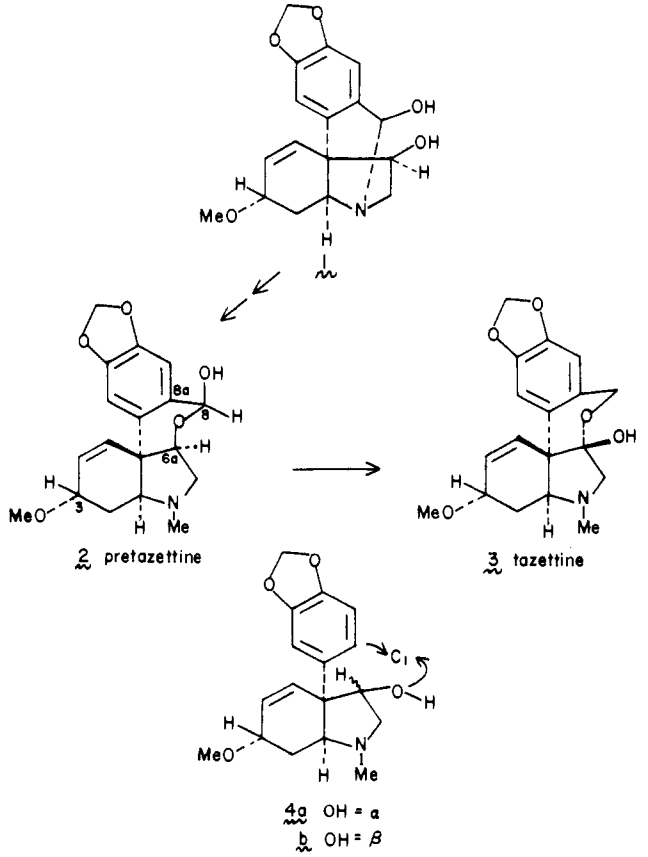
Total Synthesis of *dl*-Tazettine

Sir:

The structural relationship of the amaryllidaceae alkaloids haemanthidine (**1**) methiodide, pretazettine (**2**), and tazettine (**3**) was unveiled by Wildman and co-workers.[1,2] Shortly thereafter, Hendrickson and Fisch described a stereospecific and ingenious total synthesis of haemanthidine.[3] Given the connectivity between these alkaloids[1,2] Hendrickson's synthesis of **1** also constituted, in a formal sense, the total syntheses of **2** and **3.** Subsequent to Hendrickson's achievement, another total synthesis of *dl*-**1** was reported by Tsuda et al.[4,5] Following Wildman's protocols, racemic **1** was converted into racemic **2.**[5]

Interest in this family of alkaloids has been heightened as a consequence of the antitumor properties which have been ascribed to pretazettine by Furusawa.[6] We have thus been attempting to achieve the total syntheses of **2** and **3** by a direct strategy rather than by routes fundamentally directed toward haemanthidine. Our approach projected the synthesis of a precursor such as **4,** under the presumption that a suitable C_1 fragment (i.e., C_8)[1] could be inserted at a terminal stage between an oxygen at C_{6a} and carbon C_{8a} of the aromatic ring. It was hoped that a hydroxyl group would provide the required guidance for this operation.

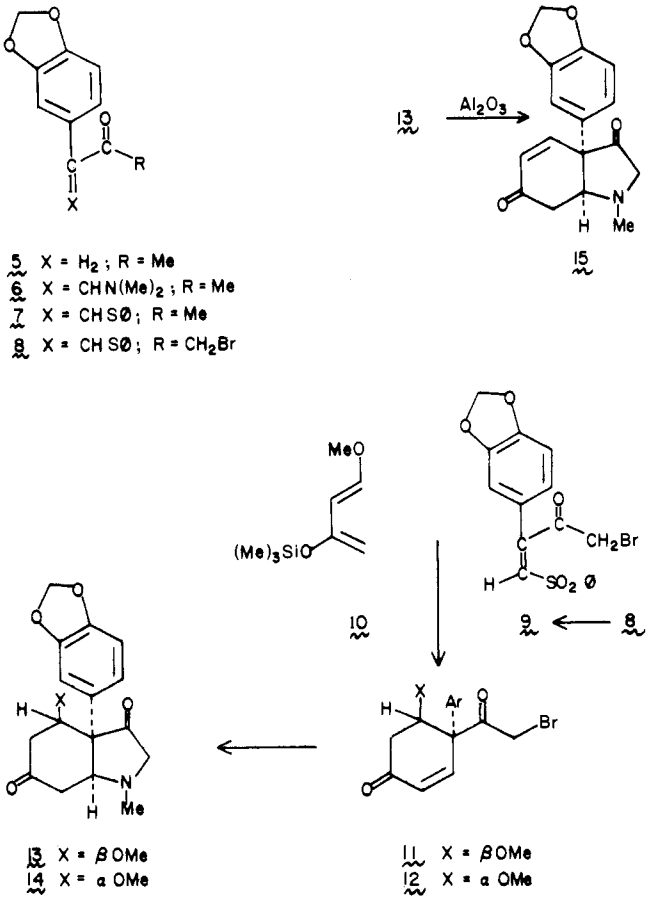
Below is provided an interim progress report on this investigation. Concise (11 steps) stereoselective constructions of both C_{6a} epimers of **4** have been realized. For the moment, we have been unable to achieve the required introduction of the C_1 unit from epimer **4b.** However, this interpolation has been accomplished via epimer **4a,** thus leading to the total syntheses of 6a-epipretazettine (**21**) and tazettine (**3**).



2 pretazettine **3** tazettine

4a OH = α
b OH = β

Our first synthetic subgoal was the enedione **15.** This compound, mp 158–159 °C, was reached in eight steps starting with the known[7] and readily available 2,3-methylenedioxyphenylacetone (**5**). Treatment of **5** with *N,N*-dimethylformamide dimethyl acetal (80 °C, 3.5 h, room temperature) afforded a quantitative yield of **6,** mp 87–88 °C,[8] which was converted in 90% yield into *E,Z* ketosulfides **7**[8] by exchange with thiophenol.[9] These were transformed into the bromomethyl sulfides **8**[8] via enol silylation [(i) LDA, THF, −78 °C; (ii) Me_3SiCl, −78 °C → room temperature] followed by bromination (*N*-bromosuccinimide). Oxidation of **8** (2 equiv of *m*-chloroperoxybenzoic acid, methylene chloride, 0 °C → room temperature) afforded the corresponding sulfones **9**[8] as a 5:1 mixture of stereoisomers in 55% yield from **7.** These sulfones were separated by chromatography on silica gel and elution with 5% ethyl acetate–benzene. The major (more polar) isomer, served as a dienophile[10a,b] toward diene **10.**[10c,d,11,12] Diels–Alder reaction was carried out at 70 °C in benzene in a sealed tube for 3 h. Chromatography on silica gel afforded a 54% yield of the 4,4-disubstituted cyclohexenones **11**[8] and **12**[8] which, after reaction with methylamine (40% aqueous solution in THF, room temperature, 30 min) afforded an 80% yield of a 9:1 mixture of **13**[8]–**14**[8]. Adsorption of **13** on neutral alumina[13] for 30 min followed by elution afforded a 45% yield of **15**[8] as well as 42% recovered **13** which are recycled in the same way.



5 X = H_2; R = Me
6 X = $CHN(Me)_2$; R = Me
7 X = CHSØ; R = Me
8 X = CHSØ; R = CH_2Br

10 **9** ← **8**

13 X = β OMe
14 X = α OMe

11 X = β OMe
12 X = α OMe

The required chiralities at carbons 3 and 6a were established as follows. The enone could be selectively reduced with diisobutylaluminum hydride in tetrahydrofuran. There was thus obtained a 3:1 ratio of alcohols **16**[8] and **17.**[8] The β-alcohol, **16,**

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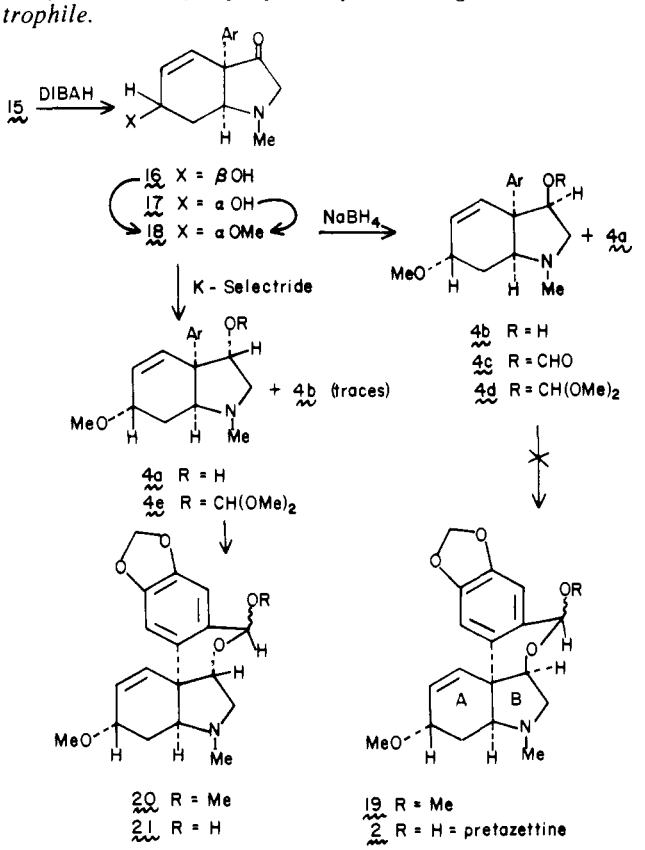
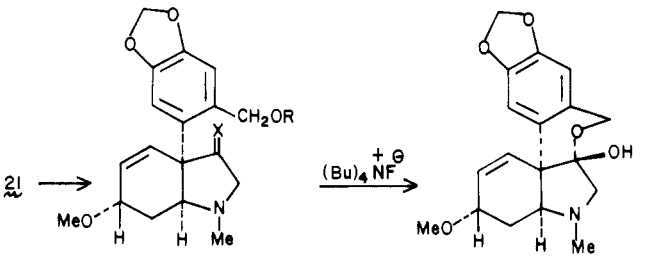
was converted into the required α-methoxy compound **18**[8] (mp 134–136 °C) by mesylation (Ms_2O, Et_3N-THF, 0 °C) followed by solvolysis in excess methanol (room temperature, 2 days).[14] The minor α-alcohol was converted into the same ether in 94% yield by reaction with diazomethane in the presence of aluminum chloride.[15] Reduction of **18** with sodium borohydride afforded a 3:1 mixture of **4b–4a.** *Conversely, reduction of* **18** *with K-Selectride in THF at 0 °C afforded a 9:1 mixture of* **4a–4b.**

We first examined the possibilities for interpolation of a C_1 formic acid equivalent in the **4b** series with a view to completing the total synthesis of pretazettine (**2**). Two approaches were followed. Intermolecular formylations (Vilsmeier Haack or dichloromethyl methyl ether) under a variety of catalytic conditions uniformly failed to provide any chromatographic or spectral support for the formation of pretazettine (**2**) or its *O*-methyl ether (**19**). Similarly unsuccessful were attempted cyclization reactions of the formate ester **4c** (a formal ring-chain valence isomer of **2**) or the mixed orthoformate **4d.** It would appear that the combination of strain associated with formation of the trans-fused B:C system in conjunction with the presence of a basic nitrogen atom and an allylic ether of only marginal stability conspire to undermine the feasibility of Lewis acid catalyzed electrophilic cyclizations.[16]

A more favorable outcome was realized in the **4a** series. Thus, reaction of **4a** with trimethyl orthoformate in the presence of 115% polyphosphoric acid at 100 °C gave, presumably via its derived mixed orthoformate **4e,**[17] a 65% yield of 6a-epipretazettine *O*-methyl ether (**20**).[8] Upon acidic hydrolysis there was obtained a quantitative yield of 6a-epipretazettine (**21**), whose NMR spectrum was identical with that published by Wildman and Bailey.[2,18] *To our knowlege this is the first example of intramolecular formylation of an aromatic ring using an alcohol for purposes of delivering the active electrophile.*



The total synthesis of tazettine was now completed as follows. Reduction of **21** with lithium aluminum hydride afforded (93%) **22.**[8] This was monoprotected (*tert*-butyldimethylsilyl chloride, triethylamine, 4-pyrrolidinopyridine, room temperature, methylene chloride) in the form of **23.**[8] Moffat Pfitzner oxidation of **23** afforded **24.** Desilylation afforded *dl*-tazettine (**3**), mp 175–176 °C (acetone), whose chromatographic mobility and infrared ($CHCl_3$), mass, and NMR ($CDCl_3$, 600 MHz) spectra were indistinguishable from those of authentic tazettine.



22 X = αOH, βH, R = H
23 X = αOH, βH, R = Si(tBu)Me2
24 X = O, R = Si(tBu)Me2

In addition to the 17-step synthesis of tazettine which has thus been completed, it is seen that this work also provides a clear entry to its C_3 epimer criwelline as well as a basis for the total syntheses of pretazettine (**2**) and precriwelline (the C_3 epimer of **2**).[19] The translation of these projections into practice as well as a more detailed examination of intramolecular aromatic substitution under the guidance of a proximate alcohol will be the objects of further research.

Acknowledgments. This research was supported by PHS Grant CA-12107-15 and 16, An Andrew Mellon Predoctoral Fellowship to J.M. and an American Cancer Society Postdoctoral Fellowship to R.G. are gratefully acknowledged. High field NMR measurements (250 and 600 MHz) were obtained on instrumentation at Mellon Institute maintained by Grant RR-00292 to the M.P.C. (Mellon-Pitt-Carnegie) Corporation. We also thank Professors P. Scheuer and E. Furusawa of the University of Hawaii for a sample of pretazettine hydrochloride.

References and Notes

(1) Wildman, W. C.; Bailey, D. T. *J. Org. Chem.* **1968,** 3749. The numbering system which we use is that proposed by Wildman.
(2) Wildman, W. C.; Bailey, D. T. *J. Am. Chem. Soc.* **1969,** *91,* 150.
(3) (a) Hendrickson, J. B.; Bogard, T. L.; Fisch, M. E. *J. Am. Chem. Soc.* **1970,** *92,* 5538. (b) Hendrickson, J. B.; Bogard, T. L.; Fisch, M. E.; Grossert, S.; Yoshimura, N. *J. Am. Chem. Soc.* **1974,** *96,* 7781.
(4) (a) Tsuda, Y.; Ukai, A.; Isobe, K. *Tetrahedron Lett.* **1972,** 3153. (b) Tsuda, Y.; Isobe, K. *Chem. Commun.* **1971,** 1555. (c) Isobe, K.; Taga, J.; Tsuda, Y. *Tetrahedron Lett.* **1976,** 2331.
(5) Tsuda, Y. *Heterocycles* **1978,** *10,* 555.
(6) (a) Furusawa, E.; Suzuki, N.; Ramanathan, S.; Furusawa, S.; Cutting, W. *Proc. Soc. Expl. Biol. Med.* **1972,** *140,* 1034. (b) Furusawa, E.; Suzuki, N.; Furusawa, S.; Lee, J. Y. B. *Ibid.* **1975,** *149,* 771. (c) Papas, T. S.; Sandhaus, L.; Chirigos, M. A.; Furusawa, E. *Biochem. Biophys. Res. Commun.* **1972,** *52,* 88. (d) Suzuki, N.; Tani, S.; Furusawa, S.; Furusawa, E. *Proc. Soc. Expl. Biol. Med.* **1974,** *145,* 771. (e) Furusawa, E.; Furusawa, S.; Lee, J. Y. B.; Patanavanich, S. *Ibid.* **1976,** *152,* 186.
(7) Biniecki, S.; Muszynski, E.; Jagiellowicz, H.; Chojnacka, Z. *Acta Polon. Pharm.* **1962,** *19,* 31; *Chem. Abstr.* **1963,** *58,* 3334g.
(8) The structure of this compound is in accord with its infrared, NMR, and mass spectral properties.
(9) Cf. Martin, S. F.; Moore, D. R. *Tetrahedron Lett.* **1976,** 4459.
(10) In this case the vinyl sulfone was found to be distinctly superior to the corresponding sulfoxides (cf. 10a and 10b) such as were used in our total synthesis of prephenic[10a] acid and griseofulvin,[10b] for reasons which will be explained in detail in a full paper on this subject: (a) Danishefsky, S.; Hirama, M.; Clardy, J.; Fritsch, N. *J. Am. Chem. Soc.* **1979,** *101,* 7013. (b) Danishefsky, S.; Walker, F. *Ibid.* **1979,** *101,* 7018. (c) Danishefsky, S.; Kitahara, T. *Ibid.* **1974,** *96,* 7807. (d) Danishefsky, S.; Kitahara, T.; Yan, C. F.; Morris, J. *Ibid.* **1979,** *101,* 6996.
(11) The major isomer is tentatively assigned to have the aryl group and hydrogen atom cis about the double bond (major isomer: $\delta_{\text{vinyl H}}$ 7.26 ppm; minor isomer: $\delta_{\text{vinyl H}}$ 6.44 ppm).
(12) The minor, less polar isomer, corresponding to **9** was found to be unreactive toward diene **10** under the conditions described for the Diels–Alder reaction.
(13) In practice, the crude 9:1 mixture of **13–14** was applied to a column of neutral alumina to effect elimination of the methoxyl group. However, the minor isomer **14** was recovered entirely unchanged by this treatment and therefore was not recycled in the same manner as **13.**

(14) Cf. Whitlock, H. W., Jr.; Smith, G. L. *J. Am. Chem. Soc.* **1967**, *89*, 3600.
(15) Muller, E.; Heischkeil; Bauer, M. *Justus Liebegs Ann. Chem.* **1964**, *677* 55.
(16) It should be emphasized that we cannot rule out the possibility that formylation of the aromatic ring might have occurred under the various reaction conditions but that other functionalities were perturbed. We can only state with certainty that in no case were we able to detect the presence of pretazettine (**2**) or its *O*-methyl ether (**19**), both of which were available to us through the courtesy of Professor P. Scheuer and Professor E. Furusawa of the University of Hawaii.
(17) The TLC (acetone) of the reaction mixture prior to the total consumation of **4a** indicated the presence of the mixed orthoformate **4e** which had been independently prepared and characterized by the reaction of **4a** with trimethylorthoformate and aluminum chloride at 100 °C. Following an aqueous workup, the TLC of the crude product showed only **20** and no trace of **4e**.
(18) Bailey, D. T. Ph.D. Thesis, Iowa State University, 1968.
(19) Sainsbury, M. "Rodd's Chemistry of Carbon Compounds", Coffey, S., Ed., Elsevier Scientific: Amsterdam, 1977; Vol. IV (B), p 165.
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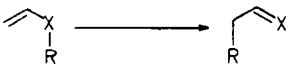
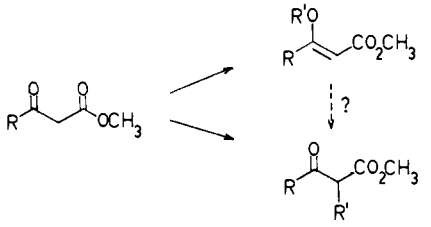
A 1,3-*O*- to -*C*-Alkyl Shift Catalyzed by Palladium

Sir:

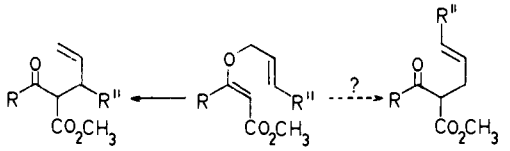
1,3-Alkyl shifts as in eq 1 represent a class of reactions that generally require rather stringent conditions to perform.[1] Such


(1)

a result stems from the requirement that, for an orbital symmetry allowed reaction, an inversion must accompany the 1,3 migration (either antarafacial with respect to the allyl unit or inversion at the migrating center) or the reaction must proceed via nonconcerted pathways. The classic contest between O and C alkylation with β-keto esters generates the need for a reac-

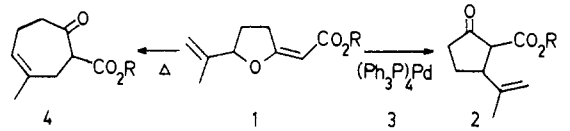


tion that would allow conversion of the O-alkylated product into the C-alkylated product. Only when R′ = allyl does such a reaction occur but with inversion of the allyl residue via a



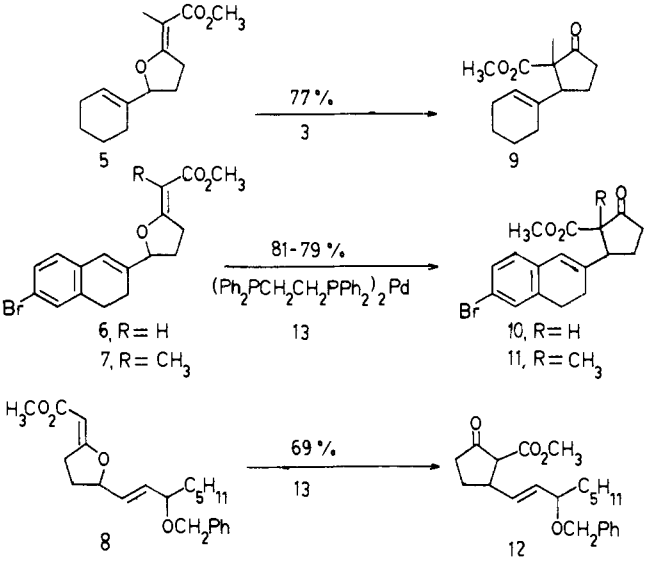
Claisen rearrangement.[2] We report herein that palladium(0) catalyzes a 1,3 shift with no allyl inversion which has led to a new cyclopentanone synthesis.

Alkylidenetetrahydrofurans such as **1** undergo thermal rearrangement to cycloheptanones (e.g., **4**) as reported by



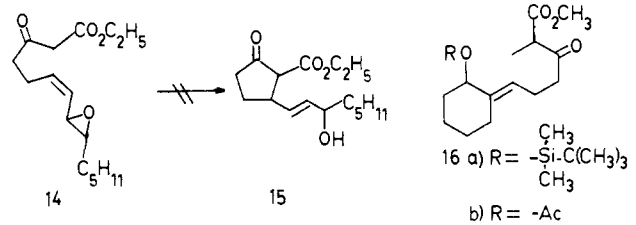
Rhoads.[3] On the other hand, subjection of **1** (R = C_2H_5) to 6 mol % of tetrakis(triphenylphosphine)palladium (**3**) in refluxing DME led to the cyclopentanone **2** (R = C_2H_5) whose spectral data compared excellently with those of an authentic sample of **2** (R = CH_3).[4] No trace of the cycloheptenone **4** was seen.

The generality of this 1,3 shift was explored with substrates **5–8**.[5,6] Isomerization of **5** to **9** with **3** as catalyst proceeded



smoothly in Me_2SO at 120 °C to give **9**[5,6,8] as a 1:1 *Z/E* mixture. Use of bis[1,2-bis(diphenylphosphino)ethane]palladium (**13**)[7] as the catalyst effected the reaction somewhat more rapidly. Performing the reaction with **3** as catalyst in DMF with the addition of anhydrous zinc chloride gave **9** in a *Z/E* ratio of 3.5:1. Interestingly, isomerizing **7** with **3** gave very poor results, whereas, using the diphos catalyst **13**, the reaction proceeded smoothly at 50 °C in Me_2SO to give **11**[5,6,8] in a 3.5:1 *Z/E* ratio. Use of pyridine-Me_2SO, acetonitrile, or DMF as solvent was somewhat less satisfactory and gave *Z/E* ratios of 2.7:1, 2:1, and 2:1, respectively. Replacing the methyl group in **7** by hydrogen, i.e., **6**, produced the isomerized product **10**[5,6] with a *Z/E* ratio of ~1:13. However, in this case, it was not possible to ascertain whether this was simply a result of equilibration of a kinetically formed product mixture. Isomerization of **8** with **13** as catalyst in dioxane gave the prostaglandin A_2 intermediate[9] **12**[5,6] in excellent yield.[10a] Use of catalyst **13** (3–6 mol %) in Me_2SO at 60 °C effected the rearrangement of **1** to **2** (R = C_2H_5) in 80% yield.

These results are especially interesting in light of the reported failure of **14** to cyclize to **15**.[9] We, too, failed in our



attempts to cyclize similar substrates—only the O-alkylated products were obtained. Indeed, treatment of **16b** with NaH or triethylamine and catalyst **3** led to O-alkylated product **5**. The alkylidene tetrahydrofuran **5** was best prepared by treatment of **16a** with 10 mol % ferric chloride in acetic anhydride[10b] (60%) at 0 °C and could then be isomerized with palladium(0) to the desired C-alkylated product **9**. Similarly, **19**, **20**, and **22**, did not undergo C alkylation, but were converted in excellent yields into the O-alkylated precursors **6**, **7**, and **8**, respectively, upon treatment with boron trifluoride etherate. Thus, this new reaction provides, in one class of substrates, a solution to the persistent problem of O vs. C al-

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