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. 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.,  $C_8$ ) 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 inves-

tigation. 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).

Our first synthetic subgoal was the enedione 15. This compound, mp 158-159 °C, was reached in eight steps starting with the known<sup>7</sup> 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 78 by exchange with thiophenol.9 These were transformed into the bromomethyl sulfides 88 via enol silylation [(i) LDA, THF, -78 °C; (ii) Me<sub>3</sub>SiCl, -78 °C  $\rightarrow$  room temperature] followed by bromination (N-bromosuccinimide). Oxidation of 8 (2 equiv of m-chloroperoxybenzoic acid, methylene chloride,  $0 \, {}^{\circ}\text{C} \rightarrow$ room temperature) afforded the corresponding sulfones 98 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 118 and 128 which, after reaction with methylamine (40% aqueous solution in THF, room temperature, 30 min) afforded an 80% yield of a 9:1 mixture of 138-148. Adsorption of 13 on neutral alumina<sup>13</sup> for 30 min followed by elution afforded a 45% yield of 158 as well as 42% recovered 13 which are recycled in the same way.

The required chiralities at carbons 3 and 6a were established as follows. The enone could be selectively reduced with disobutylaluminum hydride in tetrahydrofuran. There was thus obtained a 3:1 ratio of alcohols  $16^8$  and 17.8 The  $\beta$ -alcohol, 16,

was converted into the required  $\alpha$ -methoxy compound 18<sup>8</sup> (mp 134-136 °C) by mesylation (Ms<sub>2</sub>O, Et<sub>3</sub>N-THF, 0 °C) followed by solvolysis in excess methanol (room temperature, 2) days). 14 The minor  $\alpha$ -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<sub>1</sub> 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 ringchain 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 6aepipretazettine 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<sub>3</sub>), mass, and NMR (CDCl<sub>3</sub>, 600 MHz) spectra were indistinguishable from those of authentic tazettine.

CH<sub>2</sub>OR

CH<sub>2</sub>OR

(Bu)<sub>4</sub> NF

MeO H Me

22 X = 
$$\alpha$$
OH,  $\beta$ H, R = H

23 X =  $\alpha$ OH,  $\beta$ H, R = Si( $^{\dagger}$ Bu)Me<sub>2</sub>

24 X = O, R = Si( $^{\dagger}$ Bu)Me<sub>2</sub>

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<sub>3</sub> epimer criwelline as well as a basis for the total syntheses of pretazettine (2) and precriwelline (the C<sub>3</sub> epimer of 2).<sup>19</sup> 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.

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# 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.
  Wildman, W. C.; Bailey, D. T. J. Am. Chem. Soc. 1969, 91, 150.
  (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.; Oshimura, N. J. Am. Chem. Soc. 1974, 96, 7781.
- (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
- 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.
- 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:  $\delta_{
  m vinyl}$  H 6.44 ppm).
- The minor, less polar isomer, corresponding to 9 was found to be unreactive toward diene 10 under the conditions described for the Diels-Alder reac-
- (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.
- (20) Address correspondence to the Department of Chemistry, Yale University, New Haven, Conn. 06520.

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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. Such

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  $\beta$ -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.<sup>2</sup> 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.<sup>3</sup> On the other hand, subjection of  $1 (R = C_2H_5)$  to 6 mol % of tetrakis(triphenylphosphine)palladium (3) in re-

fluxing DME led to the cyclopentanone  $2 (R = C_2H_5)$  whose spectral data compared excellently with those of an authentic sample of  $2 (R = CH_3)$ .<sup>4</sup> No trace of the cycloheptenone 4 was seen

The generality of this 1,3 shift was explored with substrates 5-8.<sup>5,6</sup> Isomerization of 5 to 9 with 3 as catalyst proceeded

smoothly in Me<sub>2</sub>SO 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)<sup>7</sup> 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/Eratio 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<sub>2</sub>SO to give 11<sup>5,6,8</sup> in a 3.5:1 Z/E ratio. Use of pyridine-Me<sub>2</sub>SO, 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<sup>5,6</sup> with a Z/E ratio of  $\sim 1:13$ . 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<sub>2</sub> intermediate<sup>9</sup> 12<sup>5,6</sup> in excellent yield. <sup>10a</sup> Use of catalyst 13 (3-6 mol %) in Me<sub>2</sub>SO 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-