Efficient and Stereoselective Synthesis of 10-Hydroxy-4,8-dimethyldeca-3(*E*),8(*E*)-dienoic Acid, a Precursor to (3*E*,8*E*)-Suspensolide, Anastrephin, and Epianastrephin

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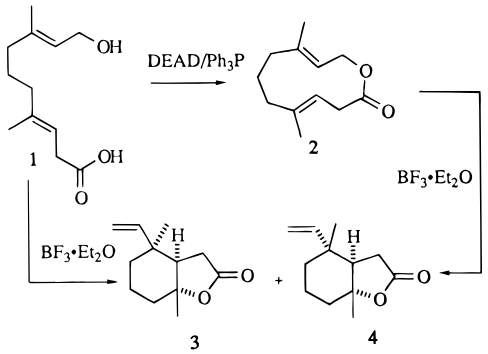
The macrolide (3*E*,8*E*)-suspensolide[1] (**2**) and the companion isomeric bicyclic lactones anastrephin[2] (**3**) and epianastrephin[2] (**4**) have been identified as major components of the male-produced pheromonal blends of the Caribbean (*Anastrepha suspensa* (Loew)) and Mexican (*Anastrepha ludens* (Loew)) fruit flies. The recent discovery[3] of a facile, essentially quantitative, rearrangement of **2** to lactones **3** and **4** under mildly acidic conditions provides a provocative biosynthetic connectivity between the three lactone components (Scheme 1).

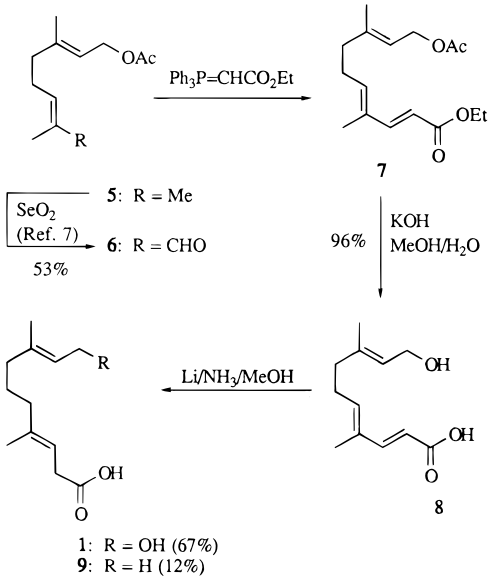
Suspensolide (**2**) has been prepared by macrolactonization of the hydroxy acid **1**.[1b,4,6] This same acid has also been shown to provide a practical route to the racemic form of lactones **3** and **4** by a BF_3-mediated cyclization/lactonization pathway.[4a,5] Two inefficient approaches to hydroxy acid **1** have been reported; a seven-step synthesis starting from mesityl oxide[1b,5] and an 18-step route from geraniol[4a] are both nonstereoselective, require tedious chromatographic separations, and produce **1** in overall yields of less than 10%. Recently, however, a report has appeared describing a seven-step synthesis of **1** from 1,6-heptadiyne in an overall yield of 22%.[6] Prompted by this report, we now wish to disclose an even shorter, highly stereoselective four-step synthesis of **1** from geranyl acetate (**5**) in an overall yield of 30% (Scheme 2).[1]

The well-exploited regioselective oxidation of the terminal *E*-methyl group of **5** with SeO_2 afforded aldehyde[7] **6** in 53% yield. Treatment of this aldehyde with ethyl (triphenylphosphoranylidene)acetate provided the acetoxy trienoic acid ester **7**.[8] The *trans*-stereochemistry of the newly introduced C2−C3 double bond was confirmed by the 2H,3H spin coupling constant ($J_{2,3}$ = 15.8 Hz). Saponification of **7** in methanol at room temperature gave the crystalline trienoic acid **8**. Harsher hydrolysis conditions led to some decomposition and consequent lower yields. The final and key step in the synthesis of hydroxydienoic acid **1** was the regio- and stereoselective reduction of the conjugated diene unit in **8** employing lithium metal in liquid ammonia in the presence of methanol to give hydroxy acid **1**. A concomitant reduction of the allylic function of **8** to give the olefinic acid **9** as a minor product was also observed under these conditions.[9] Treatment of **1** with diazomethane in ether gave the methyl ester of **1**. The IR and ^{1}H NMR spectra of **1** and its ester were virtually identical with those previously reported.[1b,4a,6] Conversion

Scheme 1



Scheme 2



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(1) (a) Chuman, T.; Sivinski, J.; Heath, R. R.; Calkins, C. O.; Tumlinson, J. H.; Battiste, M. A.; Wydra, R. L.; Strekowski, L.; Nation, J. L. *Tetrahedron Lett.* **1988**, *29*, 6561. (b) Battiste, M. A.; Rocca, J. R.; Wydra, R. L.; Tumlinson, J. H.; Chuman, T. *Tetrahedron Lett.* **1988**, *29*, 6565. (c) Rocca, J. R.; Nation, J. L.; Strekowski, L.; Battiste, M. A. *J. Chem. Ecol.* **1992**, *18*, 223.

(2) Natural anastrephin and epianastrephin isolated from cultured *A. suspensa* males are not single enantiomers, although each is enriched with the 3a(*S*),7a(*S*)-(−)-enantiomer: (a) Battiste, M. A.; Strekowski, L.; Vanderbilt, D. P.; Visnick, M.; King, R. W.; Nation, J. L. *Tetrahedron Lett.* **1983**, *24*, 2611. (b) Strekowski, L.; Visnick, M.; Battiste, M. A. *J. Org. Chem.* **1986**, *51*, 4836.

(3) Battiste, M. A.; Strekowski, L.; Coxon, J. M.; Wydra, R. L.; Harden, D. B. *Tetrahedron Lett.* **1991**, *32*, 5303.

(4) (a) Mori, K.; Nakazono, Y. *Liebigs Ann. Chem.* **1988**, 167. (b) Wydra, R. L.; Harden, D. B.; Strekowski, L.; Battiste, M. A.; Coxon, J. M. *Tetrahedron* **1992**, *48*, 3845.

(5) (a) Saito, A.; Matsushita, H.; Kaneko, H. *Chem. Lett.* **1984**, 729. (b) Saito, A.; Matsushita, H.; Kaneko, H. Jpn. Kokai Tokkyo Koho, JP 60188381, 25 Sep 1985; *Chem. Abstr.* **1986**, *104*, 109337g. (c) Saito, A.; Matsushita, H.; Kaneko, H. Jpn. Kokai Tokkyo Koko, JP 60231629, 18 Nov 1985; *Chem. Abstr.* **1986**, *104*, 148617t.

(6) Vecchio, G. H.-D.; Oehlschlager, A. C. *J. Org. Chem.* **1994**, *59*, 4853.

(7) (a) Meinwald, J.; Thompson, W. R.; Eisner, T.; Owen, D. F. *Tetrahedron Lett.* **1971**, 3485. (b) Meinwald, J.; Opheim, K.; Eisner, T. *Tetrahedron Lett.* **1973**, 281. (c) Mori, K.; Ohki, M.; Matsui, M. *Tetrahedron* **1974**, *30*, 715. (d) Kitagawa, I.; Tsujii, S.; Nishikawa, F.; Shibuya, H. *Chem. Pharm. Bull.* **1983**, *31*, 2639.

(8) A ^{1}H NMR (400 MHz) spectrum of crude **7** gave additional signals at δ 1.83 (s, 3 H), 5.61 (d, J = 12 Hz, 1 H) and 6.37 (d, J = 12 Hz, 1 H), which can be assigned to the 4-Me, 2-H, and 3-H protons, respectively, of the minor 2(*Z*),4(*E*),8(*E*)-isomer **7a**. Integration of the respective signals for **7** and **7a** indicated an isomeric ratio of ca. 20:1. For a discussion of stereoselectivity in the Wittig reaction, see: Gosey, J.; Rowley, A. G. In *Organophosphorous Reagents in Organic Synthesis*; Cadogan, J. I. G., Ed.; Academic Press: London, 1979; p 17.

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of **1** to authentic (3*E*,8*E*)-suspensolide (**2**) and the racemic form of anastrephin (**3**) and epianastrephin (**4**) was accomplished by the previously described lactonization protocols,[1b,4−6] thus providing simple five-step syntheses of these natural products.

The penultimate step in this synthesis of 3-enoic acid **1** is the reduction of 2,4-dienoic acid **8**, which is conducted under general conditions of the Birch reduction of aromatic systems.[9,10] Examples of the application of the Birch reduction to nonaromatic systems such as dienoic acids,[11] steroidal dienones,[12] and dialkylacetylenes[9] are rare. The lithium-mediated reduction of **8** is completely stereoselective in that it produces the *E*-alkene derivative **1** exclusively.

Experimental Section

^{1}H NMR (400 MHz) and ^{13}C NMR (100.6 MHz) spectra were taken in $CDCl_3$ with TMS as an internal reference. NMR peak assignments were derived from two-dimensional experiments and DEPT.

Ethyl 10-Acetoxy-4,8-dimethyldeca-2(*E*),4(*E*),8(*E*)-trienoate (7). A mixture of **6**[7] (4.2 g, 20 mmol) and ethyl (triphenylphosphoranylidene)acetate (7.7 g, 22 mmol) was heated at 100 °C under a nitrogen atmosphere for 1 h. Then the mixture was cooled and treated with ether (50 mL), and the resultant precipitate of triphenylphosphine oxide was removed by filtration. Chromatography (silica gel, AcOEt/hexanes, 1:19) gave 4.9 g (87%) of **7** as an oil: ^{1}H NMR δ 1.30 (t, J = 7.2 Hz, Me of EtO), 1.71 (s, 8-Me), 1.77 (s, 4-Me), 2.05 (s, Ac), 2.15 (t, J = 7.0 Hz, 7-H), 2.34 (q, J = 7.0 Hz, 6-H), 4.21 (q, J = 7.2 Hz, CH_2 of EtO), 4.59 (d, J = 6.8 Hz, 10-H), 5.36 (t, J = 6.8 Hz, 9-H), 5.80 (d, J = 15.8 Hz, 2-H), 5.85 (t, J = 7.0 Hz, 5-H), 7.30 (d, J = 15.8 Hz, 3-H); ^{13}C NMR δ 11.8 (4-Me), 14.0 (Me of EtO), 16.0 (8-Me), 20.2 (Me of Ac), 26.6 (C6), 38.2 (C7), 59.8 and 60.8 (C10 and CH_2 of EtO), 115.5 (C2), 119.0 (C9), 132.9 (C4), 140.4 (C5), 140.6 (C8), 148.9 (C3), 167.0 (C1), 170.5 (C=O of Ac); IR (neat) v 1712, 1738 (C=O) cm^{-1}; MS (CI with isobutane) *m*/*z* 221 (100), 281 (4, $M^+ + H$).

Anal. Calcd for $C_{16}H_{24}O_4$: C, 68.54; H, 8.63. Found: C, 68.40; H, 8.70.

10-Hydroxy-4,8-dimethyldeca-2(*E*),4(*E*),8(*E*)-trienoic Acid (8). A solution prepared from MeOH (100 mL), water (30 mL), KOH (1.9 g, 32 mmol), and **7** (2.25 g, 8 mmol) was allowed to stand at 23 °C for 72 h and then concentrated to 50 mL on a rotary evaporator and brought to pH 3 with 4 N HCl. Extraction with ether (5 × 50 mL) was followed by drying of the extract (Na_2SO_4) and removal of solvent on a rotary evaporator at 23 °C to give a white solid. Crystallizaton from MeOH/ether gave 1.61 g (96%) of **8**: mp 101−103 °C; ^{1}H NMR δ 1.70 (s, 8-Me), 1.80 (s, 4-Me), 2.14 (t, J = 7.0 Hz, 7-H), 2.36 (q, J = 7.0 Hz, 6-H), 4.17 (d, J = 7.0 Hz, 10-H), 5.44 (t, J = 7.0 Hz, 9-H), 5.80 (d, J = 15.6 Hz, 2-H), 5.92 (t, J = 7.0 Hz, 5-H), 6.5 (br s, exchangeable with D_2O, COOH and OH), 7.39 (d, J = 15.6 Hz, 3-H); ^{13}C NMR δ 12.1 (4-Me), 16.2 (8-Me), 27.0 (C6), 38.4 (C7), 59.2 (C10), 114.8 (C2), 123.9 (C9), 133.1 (C4), 138.4 (C8), 142.8 (C5), 151.5 (C3), 172.4 (C1); MS *m*/*z* 81 (100), 192 (19, $M^+ - H_2O$).

Anal. Calcd for $C_{12}H_{18}O_3$: C, 68.54; H, 8.63. Found: C, 68.20; H, 8.53.

Reduction of 8. A solution of **8** (0.67 g, 3.2 mmol) in MeOH (4 mL) was added to anhydrous liquid ammonia (40 mL) at −78 °C under a nitrogen atmosphere. The solution was stirred, allowed to reach boiling temperature, and then treated wtih finely divided lithium (0.15 g, 22 mmol) within 15 min under the reflux conditions and a constant flow of nitrogen. Removal of ammonia under a stream of nitrogen was followed by treatment of the residue with ether (100 mL) and then dropwise with water (5 mL) under constant stirring. With continuous stirring the mixture was cooled to 0 °C, acidified with 1 N HCl (5 mL), and then treated with solid NaCl (5 g). The aqueous phase was extracted with ether (3 × 20 mL), and the extracts were combined, dried (Na_2SO_4), and concentrated on a rotary evaporator. Chromatography (silica gel, AcOEt/hexanes, 1:2) gave 0.074 g (12%) of **9**, which was eluted first, and 0.45 g (67%) of **1** as oils.

The reduction of **8** with 10 equiv of lithium (0.22 g, 32 mmol) and followed by a slow evaporation of ammonia within 4 h gave **9** as the major product (53%) and **1** as the minor product (14%).

10-Hydroxy-4,8-dimethyldeca-3(*E*),8(*E*)-dienoic acid (1): ^{1}H NMR δ 1.55 (quintet, J = 7.5 Hz, 6-H), 1.63 (s, 8-Me), 1.67 (s, 4-Me), 2.01 (dt, J = 7.5 Hz, 5-H and 7-H), 3.09 (d, J = 7.2 Hz, 2-H), 4.16 (d, J = 7.0 Hz, 10-H), 5.32 (t, J = 7.0 Hz, 9-H), 5.41 (t, J = 7.2 Hz, 3-H), 7.8 (br s, exchangeable with D_2O, COOH and OH); ^{13}C NMR δ 16.0 (8-Me), 16.2 (4-Me), 25.5 (C6), 33.4 (C2), 38.9 (C5 and C7), 59.2 (C10), 115.4 (C3), 123.2 (C9), 139.3 and 139.6 (C4 and C8), 177.8 (C1); MS *m*/*z* 81 (100), 194 (8, $M^+ - H_2O$). The NMR spectra taken in C_6D_6 were virtually identical with those reported.[6]

4,8-Dimethyldeca-3(*E*),8(*E*)-dienoic acid (9): ^{1}H NMR δ 1.56 (quintet, J = 8.0 Hz, 6-H), 1.56 (d, J = 6.0 Hz, 10-H), 1.58 (s, 8-Me), 1.63 (s, 4-Me), 1.94 (t, J = 8.0 Hz, 7-H), 1.99 (t, J = 8 Hz, 5-H), 3.09 (d, J = 7.0 Hz, 2-H), 5.20 (q, J = 6.0 Hz, 9-H), 5.31 (t, J = 7.0 Hz, 3-H); ^{13}C NMR 13.2 (C10), 15.4 (8-Me), 16.2 (4-Me), 25.9 (C6), 33.4 (C2), 39.0 and 39.1 (C5 and C7), 114.8 (C3), 118.4 (C9), 135.3 (C8), 139.8 (C4), 179.1 (C1); MS *m*/*z* 82 (100), 196 (8, M^+).

Anal. Calcd for $C_{12}H_{20}O_2$: C, 73.42; H, 10.27. Found: C, 73.51; H, 10.30.

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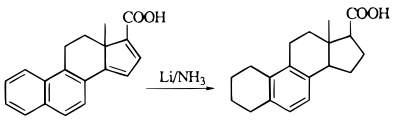
(9) For selected reviews of the Birch reduction, see: (a) House, H. O. *Modern Synthetic Reactions*, 2nd ed.; W. A. Benjamin, Inc.: Menlo Park, CA, 1972; p 145. (b) Birch, A. J.; Smith, H. *Q. Rev. Chem. Soc.* **1978**, *12*, 17.

(10) (a) Birch, A. J.; Slobbe, J. *Tetrahedron Lett.* **1975**, 627. (b) Masamune, T.; Ono, M.; Matsue, H. *Bull. Chem. Soc. Jpn.* **1975**, *48*, 491. (c) Divanfard, H. R.; Joullie, M. M. *Org. Prep. Proc. Int.* **1978**, *10*, 94.

(11) (a) Birch, A. J.; Slobbe, J. *Aust. J. Chem.* **1976**, 29, 2737. (b) Balme, G. *Tetrahedron Lett.* **1985**, 26, 2309. (c) Of interest is ref 4 (Wilds, A. L. Personal communication) in the reference by Caine (Caine, D. *Org. React.* **1976**, *23*, 219), which states that reduction of dienoic acid (i) with lithium in liquid ammonia results in complete saturation of the diene system to give (ii).



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(12) Dryden, H. L., Jr. In *Organic Reactions in Steroid Chemistry*; Fried, J., Edwards, J. A., Eds; Van Nostrand Reinhold Co.: New York, NY, 1972; Vol. 1, p 1.