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SHORT, REGIO- AND STEREO-SELECTIVE PREPARATION OF 1,5- AND 1,6-DIENES. SYNTHESES OF *EUDIA PAVONIA* PHEROMONE AND GOSSYPLURE.

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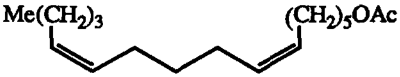
Abstract : Two pheromones, (Z)-6,(Z)-11-hexadecadien-1-yl acetate (from *Eudia pavonia*) and gossyplure, have been synthesized each by two consecutive sequences of nickel-assisted Grignard reactions with cyclic enol ethers and the preparation of Grignard reagents from the resultant alcohols, followed each by copper-promoted Grignard reaction with a small-ring ether and subsequent acetylation.

A few years ago a new method of carbon-carbon bond formation with great potential for rapid, regio- and stereo-selective preparation of olefins was introduced, based on nickel-catalyzed interaction of Grignard reagents with enol ethers.[1] This procedure appeared ideally suited for the construction of straight-chain polyen-1-ols (or acetates), compounds wich abound in nature, especially as insect sex pheromones.[2] The following presentation illustrates the utilization of the method for the synthesis of *Eudia pavonia* pheromone (**1**)[3] and gossyplure (a 1:1 **2**-**3** mixture).[4]



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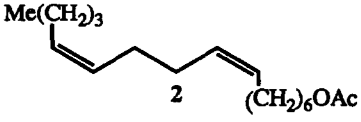

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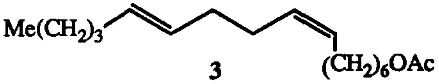

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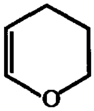
The methyl-terminating portions of the dienyl acetates were built up in the following manner. Exposure of dihydropyran (**4**) to *n*-butylmagnesium bromide in 4:1 toluene-ether (room temperature, 96 h) in the presence of bis(triphenylphosphino)nickel dichloride ($(tpp)_2NiCl_2$) led to 4-penten-1-ol and (*Z*)-4-nonen-1-ol[1d,4e,h,5,6] (**6a**) in 15 and 68% yield, respectively.[7,8,9] Interaction of 2,3-dihydrofuran (**5**) with *n*-butylmagnesium bromide in toluene (-10°C, 96 h) under the influence of $(tpp)_2NiCl_2$ gave (*Z*)-3-octen-1-ol[4f,5] (**7a**) in 30% yield,[7] whereas the same reaction (80°C, 20 h) induced by [1,3-bis(diphenylphosphino)propane]nickel dichloride ($(dppp)NiCl_2$) afforded a ca. 2.3:1 mixture of (*E*)- (**8a**)[4f] and (*Z*)-3-octen-1-ol (**7a**) in 75% yield.[7] Treatment of alcohols **6a** and **7a** with trifluoroacetic acid anhydride (tetrahydrofuran, 20°C) and thereafter with lithium bromide (2.5:1 tetrahydrofuran-dimethylformamide, 80°C)[10,11] produced bromides **6b**[4e,f] (99%) and **7b**[4f] (99%), respectively.



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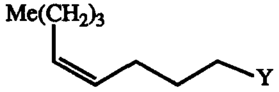

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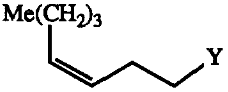

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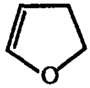
a, Y = OH; **b**, Y = Br;



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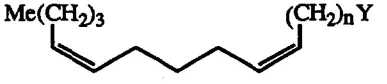
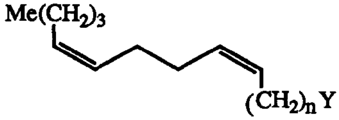
Conversion of bromide **6b** into a Grignard reagent (72%) with magnesium in ether and interaction with dihydropyran (**4**) under the conditions (72 h) of the above preparation of alcohol **6a** afforded (*Z*)-4,(*Z*)-9-tetradecadien-1-ol (**9a**) (38%). Transformation of the latter into its bromide (**9b**) (99%) under the above **6a** —>**6b** reaction conditions, formation of a Grignard reagent (68%) and exposure thereof to cuprous iodide and ethylene oxide (ether, room temperature)[12] yielded (*Z*)-6,(*Z*)-11-hexadecadien-1-ol (**9c**)[3] (60%). Acylation of the alcohol with acetic anhydride and pyridine furnished (99%) the *Eudia pavonia* pheromone (**1**).



9a, n = 3, Y = OH
b, n = 3, Y = Br
c, n = 5, Y = OH



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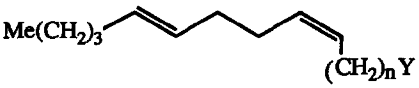

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a, $n = 3$, $Y = OH$
b, $n = 3$, $Y = Br$
c, $n = 6$, $Y = OH$

Formation of a Grignard reagent (65%) from bromide **7b** and magnesium in ether and exposure of the reagent to dihydropyran (**4**) and $(tpp)_2NiCl_2$ in toluene (room temperature, 72 h) gave (Z)-4,(Z)-8-tridecadien-1-ol (**10a**)[3,4d] (30%), whose quantitative conversion into its bromide (**10b**) followed the above **7a**—>**7b** procedure. Cuprous iodide-assisted interaction of the Grignard reagent (75%) with oxetane[12] produced (Z)-7,(Z)-11-hexadecadien-1-ol (**10c**)[3] (75%). Repetition of the **7a**—>**7b**—> **10a**—>**10b**—>**10c** reaction sequence starting with the **8a-7a** mixture yielded a ca. 2.3:1 mixture of alcohols **11c**[3,4] and **10c**[3,4], respectively, whose dilution with the requisite amount of pure hexadecadienol **10c** led to a 1:1 **10c-11c** alcohol mixture. Acylation of the latter with anhydride and pyridine yielded quantitatively gossyplure (1:1 **2-3**).

The purity of the above synthetic intermediates was ascertained by glc analysis and confirmed by ^{13}C NMR spectral determination.[13] Except for the reported mixtures of reaction products each compound was >97% stereochemically pure. The present method of pheromone synthesis is much briefer than previously recorded procedures, e.g. the one-step preparation of olefinic alcohol **6a** having required earlier many reactions. Finally, the above reaction schemes can be executed on large scale (e.g. 20 g).

References and Notes

1. (a) E. Wenkert, E.L. Michelotti, and C.S. Swindell, *J. Am. Chem. Soc.*, 1979, **101**, 2246. (b) E. Wenkert and T.W. Ferreira, *Organometallics*, 1982, **1**, 1670. (c) E. Wenkert, E.L. Michelotti, C.S. Swindell, and M. Tingoli, *J. Org. Chem.*, 1984, **49**, 4894. (d) E. Wenkert, V.F. Ferreira, E.L. Michelotti, and M. Tingoli, *J. Org. Chem.*, 1985, **50**, 719.

2. The method has been utilized recently for the synthesis of natural products of other types : (a) R. Whitby, C. Yeates, P. Kocienski, and G. Costello, *J. Chem. Soc., Chem. Commun.*, 1987, 429. (b) P. Kocienski and S. Wadman, *J. Org. Chem.*, 1989, **54**, 1215.

3. H.J. Bestmann, K.H. Koschatzky, and O. Vostrowsky, *Liebigs Ann. Chem.*, 1982, 1478.

4. (a) For previous syntheses see *inter alia* (a) ref. 3. (b) P.E. Sonnet, *J. Org. Chem.*, 1974, **39**, 3793. (c) K. Mori, M. Tominaga, and M. Matsui, *Tetrahedron*, 1975, **31**, 1846. (d) R.J. Anderson and C.A. Henrick, *J. Am. Chem. Soc.*, 1975, **97**, 4327. (e) H.J. Bestmann, K.H. Koschatzky, W. Stransky, and O.Vostrowsky, *Tetrahedron Lett.*, 1976, 353. (f) H. Disselnkötter, K. Eiter, W. Karl, and D. Wendisch, *Tetrahedron*, 1976, **32**, 1591. (g) T. Ishihara and A. Yamamoto, *Agric. Biol. Chem.*, 1984, **48**, 211 (h) N.N. Joshi, V.R. Mandapur, and M.S. Chahdha, *Tetrahedron*, 1984, **40**, 3285. (i) I. Andelic, F. Myhren, and L. Skattebol, *Acta Chim. Scand.*, 1985, **B39**, 231.

5. *Inter alia* H.J. Bestmann, K.H. Koschatzky, W. Schätzke, J. Süsz, and O. Vostrowsky, *Liebigs Ann. Chem.*, 1981, 1705.

6. G. Ohloff, C. Vial, F. Näf, and M. Pawlak, *Helv. Chim. Acta*, 1977, **60**, 1161.

7. The yields of all Grignard reactions are based on the quantity of RMgX used.

8. The exclusivity of *cis* isomer formation was due to the low reaction temperature. Elevated temperature leads to a mixture of *Z* and *E* isomers[1a] (see also D.A. Carlson and T.L. Davis, *Synthesis*, 1989, 936.)

9. Repetition of the (dppp)$NiCl_2$-promoted reaction (benzene, 70°C, 20 h), reported earlier[1d], furnished a ca. 3.5:1 4-nonen-1-ol *E*/*Z* mixture (35%).

10. *Cf.* F. Camps, V. Gasol, and A. Guerrero, *Synthesis*, 1987, 511.

11. All reactions leading to or emanating from olefinic bromides were carried out in darkness. The acylation and halide displacement constituted a "one-pot" reaction process.

12. C. Huynh, F. Derguini-Boumechal, and G. Linstrumelle, *Tetrahedron Lett.*, 1979, 1503.

13. R. Rossi, A. Carpita, M.G. Quirici, and C.A. Veracini, *Tetrahedron*, 1982, **38**, 639.

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