ORGANIC LETTERS

1999
Vol. 1, No. 6
845−848

A Convergent and Highly Efficient Synthesis of (*E,Z*)-2,13-Octadecadienyl Acetate and (*E,Z*)-3,13-Octadecadienyl Acetate, Components of the Sex Pheromone of the Leopard Moth *Zeuzera pyrina*, through Sulfones

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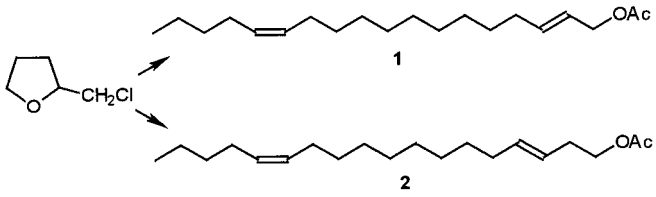
Received June 1, 1999

ABSTRACT



A new, convergent synthesis of (*E,Z*)-2,13-octadecadienyl acetate (1) and (*E,Z*)-3,13-octadecadienyl acetate (2), the two key components of the leopard moth *Zeuzera pyrina*, from 2-chloromethyltetrahydrofuran in good overall yields and stereomeric purity is reported. The synthesis of both components utilizes the common intermediate sulfone 12 as a convenient building block to be coupled with iodoacetylenic derivatives 9 or 17 in the key step.

The leopard moth *Zeuzera pyrina* is a very important wood borer of forest and fruit trees of worldwide distribution. The sex pheromone of the moth was identified as mixture of (*E,Z*)-2,13-octadecadienyl acetate (**1**), (*E,Z*)-3,13-octadecadienyl acetate (**2**), and (*Z*)-13-octadecenyl acetate.[1,2] Analysis of the sex pheromone glands of our strain, collected in the field, confirmed the presence of the three components in an 86:4:10 ratio, respectively.[3] Compound **2** is a component of the lesser peachtree borer *Synanthedon pictipes* and the peachtree borer *Sanninoidea exitiosa*[4a] and synergizes the effect of **1** in the currant borer *Synanthedon tipuliformis* pheromone[4b] (Figure 1).

So far, a number of syntheses of both compounds and their geometric isomers have been reported, based on alkylation reactions of terminal acetylene intermediates with the

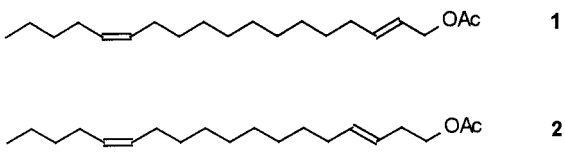


Figure 1. Structures of the two key components of the sex pheromone of the leopard moth *Z. pyrina*.

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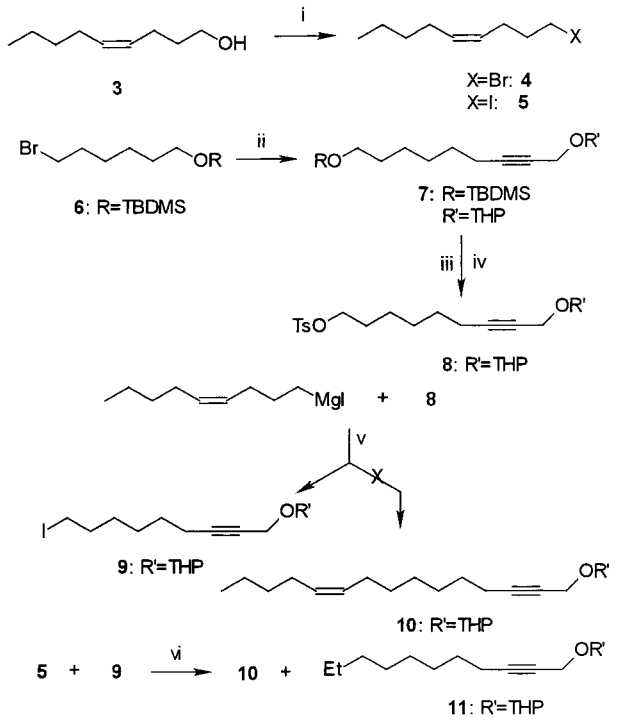
10.1021/ol990114j CCC: $18.00
Published on Web 08/31/1999

required alcohol-protected synthons,[2,4a,5−7] Grignard reaction of a long-chain protected bromo alcohol with an allylic bromide in the presence of Li_2CuCl_4,[8] selective alkylation reactions of (*Z*)-3-hexene-1,6-diol,[9] selective isomerization of one triple bond of a diynol,[10] two sequential carbocupration reactions of acetylene,[11] Pd-catalyzed alkylation of a organozinc intermediate with a iodoalkene,[12] and opening of alkenyl cyclopropenyl ketones.[13] However, some of them show low stereoselectivity and others afford low overall yields for preparative purposes,[10,13] and to our knowledge, neither of them is convergent. Therefore, a convergent, and stereoselective synthesis, amenable for preparative applications, is still needed. In this paper, we report a convenient synthesis of compounds **1** and **2** that fulfills these requirements.

Alkenol **3** was prepared by hydrogenation (Pd Lindlar/quinoline) at −10 °C in hexane of 4-nonynol, obtained from 2-chloromethyltetrahydrofuran.[14] Under these conditions, compound **3** was obtained in >99.5% stereomeric purity and 53% overall yield after column chromatography. This procedure was clearly superior to the elegant method of ring opening of 3,4-dihydropyran by the Grignard reagent of *n*-butyl bromide in the presence of $(tpp)_2NiCl_2$ as catalyst[15] (20% yield, *Z*:*E* 96:4).

Elongation of the chain was initially tried by coupling of the Grignard reagent of iodide **5**[16] with tosylate **8**, obtained in turn by alkylation of THP-protected propargyl alcohol with TBDMS-protected bromohexanol **6**, in the presence of Li_2CuCl_4. The reaction failed to produce the coupling product **10** furnishing, unexpectedly but univocally, iododerivative **9** in 66% yield. To our knowledge, this type of reaction is unprecedented and was confirmed with other model tosylates, implying a possible nucleophilic iodide-copper species responsible for the nucleophilic displacement of the tosylate. Equally unsuccessful was the reaction of the organocuprate derivative of **5** (2.2 equiv of *t*-BuLi/CuI in pentane/ether 3:2) with **8**, while reaction of the organozinc derivative of **5** with **9** in the presence of $Me_2Cu(CN)(MgCl)_2$ in THF:DMPU[17,18] provided the expected compound **10** along with **11** in 46:54 ratio (Scheme 1). This mixture was inseparable, so an alternative approach was undertaken.

Scheme 1



i: (a) $(CF_3CO)_2O$/THF, rt 20 min, (b) LiX (5 equiv.)/THF:HMPA (1:1), reflux, 2 h; ii: $HC{\equiv}CCH_2OTHP$, BuLi/THF 0 °C then rt, 3 h/addn. **6**/THF:HMPA 1:1, 0 °C, 2 h, 85%; iii: Al_2O_3 3% H_2O, rt 20 h, 75%; iv: TsCl/py 0 °C, 16 h, 46%;v: Li_2CuCl_4/THF -70 °C, then rt 12 h, 66% vi: $2Et_2Zn$, CuI, 60 °C, 16 h, added to $Me_2Cu(CN)(MgCl)_2$/THF, 0 °C, addn. **9**/DMPU -78 °C, then 0 °C 2 h

Alkylation of sulfone-mediated carbanions has been well documented,[19,20] and accordingly, sulfone **12** was considered a good substrate to construct the C-18 chain. Transformation of **3** into bromide **4** was carried out through the intermediate formation of the trifluoroacetate ester as leaving group, in a convenient one-step process.[16] We feel that our procedure is shorter and at least as efficient as the classical mesylation/tosylation process. Compund **4** was reacted with sodium benzenesulfinate in DMF providing sulfone **12** in 81% yield, along with 11% of the corresponding phenyl sulfinate ester, after column chromatography purification. Utilization of benzenesulfinate anion supported on Amberlyst A-26 resin to minimize sulfinate ester formation[21] or Dowex 1-X gave in our hands inferior results (36−43% of **12** along with 18% of phenyl sulfinate). The other synthon required was iodide **9**, which was obtained by two routes: (a) selective hydrolysis of the TBDMS group of acetylene **7** with neutral alumina[22,23]

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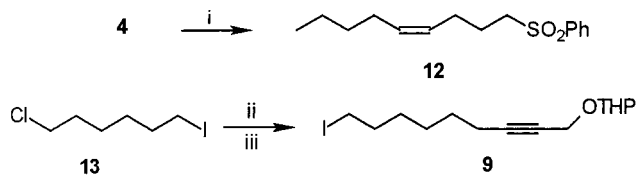
followed by iodination of the resulting alcohol[16] (49% overall) and (b) propargylation reaction of 1-chloro-6-iodohexane (**13**) followed by iodination (87% overall yield after purification on column chromatography) (Scheme 2).

Scheme 2

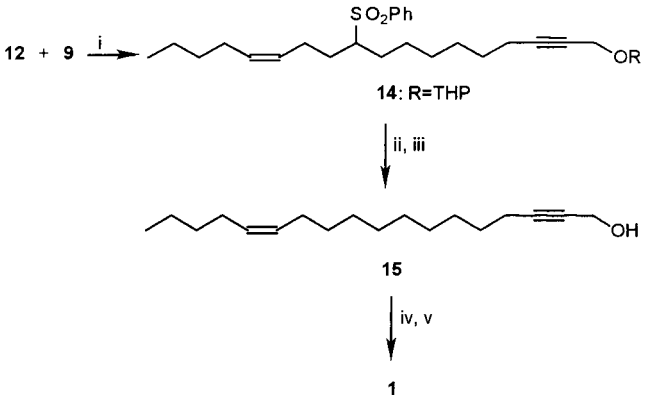


i: NaPhSO$_2$/DMF, 110 °C, 4 h, 81%; ii: HC≡CCH$_2$OTHP, BuLi/THF, 0 °C then rt, 3 h/addn. **13**/THF:HMPA 1:1, 0 °C, 2 h, 60%; iii: NaI/Me$_2$CO, reflux, 48 h, 87%

Coupling reaction of iodide **9** with sulfone **12** was assayed under different conditions, since in preliminary trials the bis-alkylation reaction became an important secondary reaction, as has been noticed previously.[24] *Formation of the bis-alkylated compound, under experimental conditions expected to give monoalkylation products, may limit the synthetic utility of the sulfone-mediated alkylation processes.* We have found that *n*-BuLi or NaH in THF/HMPA or THF/DMPU are not good bases to promote monoalkylation of sulfone **12** selectively, while LDA (2 equiv) in THF/HMPA 10:1 at −50 °C[25] led to **14**, exclusively, in an excellent 98% isolated yield after chromatographic purification. After hydrolysis of the THP group, desulfonylation of the resulting alcohol was effected with Na amalgam in MeOH in the presence of Na_2HPO_4[26] to provide alcohol **15** in 88% yield after column chromatography. Reduction of **15** with LAH in diglyme at reflux[14] occurred in unsatisfactory low yield and stereochemical purity, but simple replacement by THF as solvent at reflux provided the corresponding dienol in 91% yield with a stereomeric purity of the new double bond $E \geq 99.5\%$. Acetylation of the alcohol under standard conditions led to acetate **1** in 90% yield after purification by column chromatography (26.8% overall from 2-chloromethyltetrahydrofuran) with a stereochemical purity of 98% *Z* and ≥99.5% *E* of the double bonds at C-13 and C-2, respectively, by GC capillary column (Scheme 3).[27]

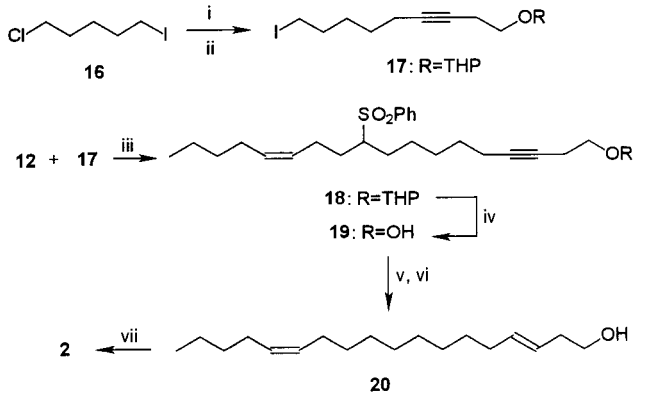
In a similar manner, reaction of 1-chloro-5-iodopentane (**16**) with THP-protected propargyl alcohol followed by replacement of chlorine by iodine afforded pure **17** after column chromatography (27.1% overall yield). Then, coupling reaction of sulfone **12** with iodo derivative **17** under conditions similar to those for compound **14** (see above) led to monoalkylated sulfone **18** (66% after purification by column chromatography), without concomitant formation of the bis-alkylated poduct. Compund **18** was hydrolyzed to the corresponding alcohol and desulfonylated with sodium amalgam as above to obtain the expected enyne alcohol in 81.5% overall yield after silica gel chromatography. Conventional reduction of the triple bond to the *E* olefin furnished dienic alcohol **20**, which upon acetylation under standard conditions led to acetate **2** (78.8% isolated yield after column chromatography purification) (13.5% overall from 2-chloromethyltetrahydrofuran) (Scheme 4). Stereochemical purity of the compound was >98% *E*, 94% *Z* by GC capillary column and ^{13}C NMR.[27]

Scheme 3



i: LDA (2 equiv.)/THF:HMPA 10:1, -78 °C, then -50 °C, 4 h, 98%; ii: p-TsOH/MeOH, rt, 16 h, 92%; iii: Na(Hg) 5% (10 equiv.), Na$_2$HPO$_4$ (10 equiv.)/MeOH, -10 °C, then rt, 21 h, 88%; iv: LAH/THF, 91%; v:Ac$_2$O,Et$_3$N, DMAP/CH$_2$Cl$_2$, 90%

Scheme 4



i: HC≡CCH$_2$OTHP, BuLi/THF, 0 °C then rt, 30 min/addn. **16**/THF:HMPA 1:1, 0 °C, then rt 2 h, 33%; ii: NaI/Me$_2$CO, reflux, 48 h, 82%; iii: LDA (3 equiv.)/THF:HMPA 10:1, -78 °C, then -50 °C 2h, 66%; iv: p-TsOH/MeOH, 0 °C, then rt 16 h, 84%; v: Na(Hg) 5% (10 equiv.), Na$_2$HPO$_4$ (10 equiv.)/MeOH -10 °C, then rt 21 h, 97%; vi: Na, NH$_3$/THF 4 h, 83%; vii: Ac$_2$O, Et$_3$N, DMAP/CH$_2$Cl$_2$, 95%

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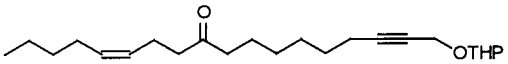
(25) When the reaction was carried out at −78 °C, the ketone resulting from oxidative desulfonylation of **14** was also obtained, as determined by its spectral properties.



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In summary, we have developed a new and stereoselective, highly efficient synthesis of the two key components of the sex pheromone of the leopard moth in high overall yield and stereomeric purity. Our method, being fully convergent, complements the procedures already described in the literature for preparation of both compounds. The compounds were electrophysiologically (EAG) active[3] and blended in adequate proportions found to be highly attractive to males in the field. The results will be reported in due course.

Acknowledgment. We thank CIRIT (Generalitat de Catalunya) and KenoGard, S.A. for a predoctoral fellowship to A.C. and C.Q. and I.P, respectively, and CICYT (AGF95-0185, AGF97-1217-C02-01) and Comissionat per a Universitats i Recerca (1997SGR-00021) for financial support. We also gratefully acknowledge Prof. P. Knochel for accepting A.C. in his laboratory, his advice, and his review of the manuscript.

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(27) Spectroscopic and analytical features of **1** and **2**. **1**: IR (film) ν 2923, 2854, 1743, 1463, 1378, 1361, 1228, 1023, 967, 721 cm^{-1}; ^1H NMR (300 MHz) δ 5.77 (dt, $J = 15.3$, $J' = 6.9$ Hz, 1H), 5.55 (dtt, $J = 15.3$, $J' = 6.6$, $J'' = 1.5$ Hz, 1H), 5.4−5.25 (m, 2H), 4.5 (d, $J = 6.3$ Hz, 2H), 2.06 (s, 3H), 2.1−1.9 (c, 6H), 1.42−1.2 (c, 18H), 0.89 (t, $J = 6.9$ Hz, 3H) ppm; ^{13}C NMR (75 MHz) δ 170.9, 136.7, 129.8 (2C), 123.6, 65.3, 32.2, 31.9, 29.7, 29.54, 29.52, 29.4, 29.3, 29.16, 28.9, 27.2, 26.9, 22.3, 21.0, 13.99 ppm; MS (*m*/*z*) 248 ($M^+ - 60$, 4), 177 (2), 163 (3), 149 (7), 135 (7), 121 (17), 109 (27), 96 (48), 95 (49), 82 (50), 81 (66), 69 (33), 68 (35), 67 (68), 55 (100). Anal. Calcd for $C_{20}H_{36}O_2$: C, 77.87; H, 11.78. Found: C, 77.87; H, 11.82. **2**: IR (film) ν 2954, 2925, 2854, 1745, 1465, 1456, 1236, 1035, 968, 732 cm^{-1}; ^1H NMR (300 MHz) δ 5.50 (dt, $J = 15.3$, $J' = 6.6$ Hz, 1H), 5.41−5.28 (m, 3H), 4.06 (t, $J = 6.9$ Hz, 2H), 2.3 (m, 2H), 2.04 (s, 3H), 2.08−1.93 (c, 6H), 1.4−1.2 (c, 16H), 0.89 (t, $J = 6.9$ Hz, 3H) ppm; ^{13}C NMR (75 MHz) δ 171.1, 133.6, 129.85, 129.84, 124.92, 64.14, 32.59, 31.95, 31.93, 29.74, 29.49, 29.37, 29.28, 29.11, 27.17, 26.9, 22.33, 20.98, 13.99 ppm; MS (*m*/*z*) 248 (M^+-60, 4), 219 (2), 205 (2), 191 (2), 177 (2), 163 (4), 149 (8), 135 (16), 121 (18), 109 (25), 96 (44), 95 (49), 82 (52), 81 (75), 69 (31), 68 (47), 67 (89), 55 (100), 54 (49). Anal. Calcd for $C_{20}H_{36}O_2$: C, 77.87; H, 11.78. Found: C, 77.88; H, 11.90.