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of Reliable Methods
for the Preparation
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September 2014: The paragraphs above replace the section "Handling and Disposal of Hazardous Chemicals" in the originally published version of this article. The statements above do not supersede any specific hazard caution notes and safety instructions included in the procedure.

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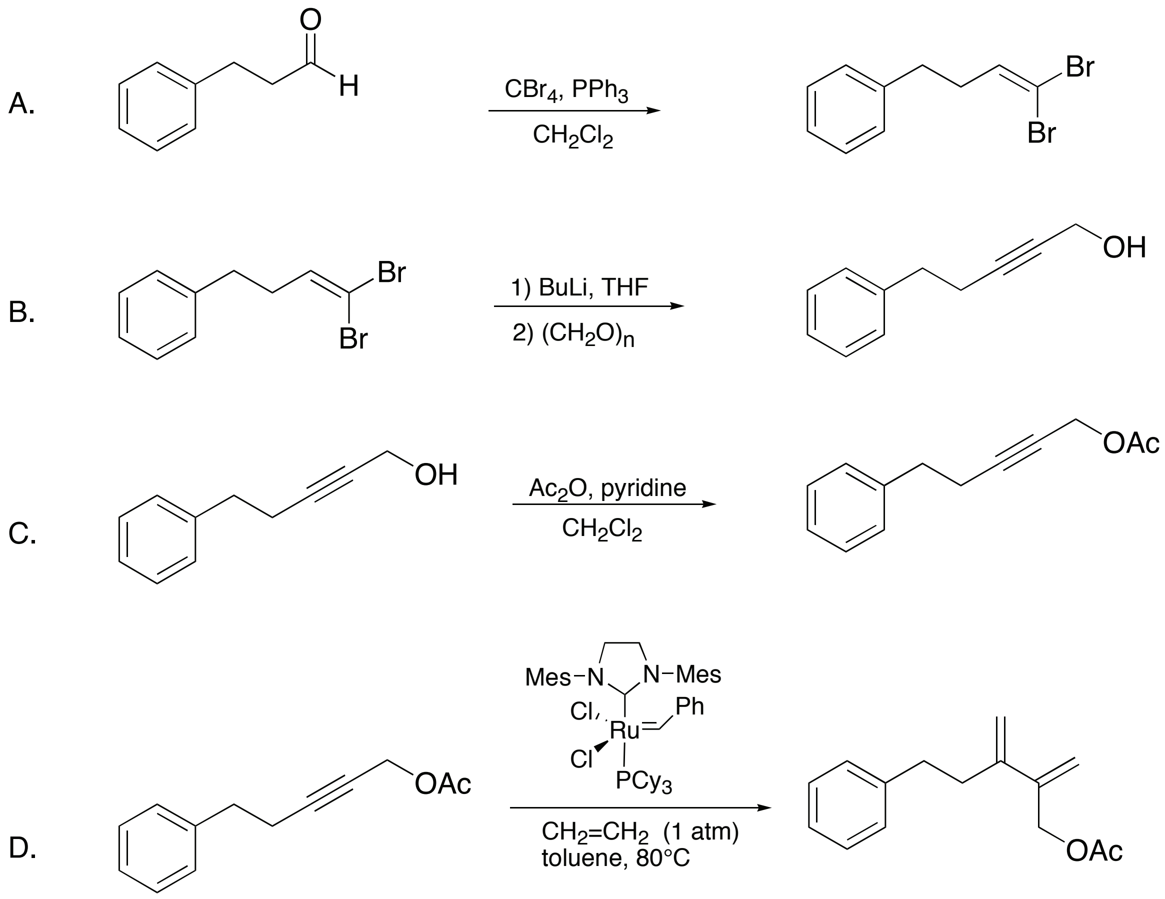
SYNTHESIS OF 1,3-DIENES FROM ALKYNES AND ETHYLENE: ACETIC ACID 2-METHYLENE-3-PHENETHYLBUT-3-ENYL ESTER

[Benzenepentanol, β,γ-bis(methylene)-, acetate]



Submitted by Miwako Mori, Keisuke Tonogaki, and Atsushi Kinoshita.[1]
Checked by Scott E. Denmark and Tetsuya Kobayashi.

1. Procedure

A. (4,4-Dibromobut-3-enyl)benzene. A flame-dried, 2-L, three-necked flask, equipped with a magnetic stirbar, a rubber septum, an addition funnel fitted with a rubber septum, and an argon inlet is charged with 82.46 g (248.64 mmol) of carbon tetrabromide (Note 1) and then 400 mL of anhydrous dichloromethane (CH_2Cl_2, Note 2) is added by syringe. The solution is cooled in an ice-water bath and a solution of 130.43 g (497.28 mmol) of triphenylphosphine (Note 3) in 400 mL of anhydrous CH_2Cl_2 is then added dropwise via the addition funnel over 30 min. The reaction mixture is stirred at 0 °C for 10 min, and then a solution of 16.4 mL (16.7 g, 124.3 mmol) of 3-phenylpropionaldehyde (Note 4) in 266 mL of anhydrous CH_2Cl_2 is added over 10 min via cannula. The solution is stirred at 0 °C for 1 h, and then 500 mL of H_2O is added. The resulting mixture is transferred to a 4-L separatory funnel and the aqueous layer is separated and extracted with three 200-mL portions of CH_2Cl_2. The combined organic layers are washed with 600 mL of brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure using a rotary evaporator. To the residue is added 500 mL of diethyl ether, and the resulting suspension is filtered to remove triphenylphosphine oxide. The solid that is collected is washed with three 300-mL portions of diethyl ether, and the combined ethereal filtrate is concentrated under reduced pressure using a rotary evaporator. The residue is purified by flash column chromatography on 500 g of silica gel (elution with hexane/ether, 10:1). The fractions containing the product are collected and concentrated under reduced pressure using a rotary evaporator to yield 34.75 g (96%) of (4,4-dibromobut-3-enyl)benzene as a colorless oil (Note 5).

B. 5-Phenylpent-2-yn-1-ol. A flame-dried, two-necked, 1-L, round-bottomed flask equipped with an argon inlet, rubber septum, and a magnetic stirbar is charged with (4,4-dibromobut-3-enyl)benzene (30.00 g, 103.45 mmol) and then anhydrous tetrahydrofuran (345 mL) (Note 6) is added to the flask by syringe. The reaction mixture is cooled in a –78 °C dry ice-acetone bath while a solution of *n*-butyllithium in hexane (1.6M, 148 mL, 237 mmol) (Note 7) is added via syringe over 30 min. The solution is stirred at –78 °C for 30 min, and then paraformaldehyde (9.32 g, 310.35 mmol) (Note 8) is added in one portion. The solution is stirred at –78 °C for 30 min, and then allowed to warm to room temperature and stirred for 1 h. Saturated aqueous NH_4Cl (400 mL) is added and the aqueous layer is separated and extracted with three 200-mL portions of ethyl acetate. The combined organic layers are washed with 400 mL of brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure using a rotary evaporator. The residue is purified by flash column chromatography on 500 g of silica gel (elution with hexane/ethyl acetate, from 7:1 to 1:1). The fractions containing the product are collected and concentrated under reduced pressure using a rotary evaporator to yield 14.32 g (86%) of 5-phenylpent-2-yn-1-ol (Note 9) as a colorless oil.

C. Acetic acid 5-phenylpent-2-ynyl ester. A flame-dried, 500-mL, three-necked, round-bottomed flask equipped with an argon inlet, two rubber septa, and a magnetic stirbar is charged with 5-phenylpent-2-yn-1-ol (13.51 g, 84.33 mmol) and then 280 mL of anhydrous CH_2Cl_2 is added by syringe. The solution is cooled in an ice-water bath and pyridine (68 mL, 843 mmol) (Note 10) is added in one portion by syringe, followed by the addition of acetic anhydride (32 mL, 337 mmol) (Note 11) over 10 min. The reaction mixture is stirred at room temperature overnight. The mixture is cooled to 0 °C, 10.3 mL of MeOH is added, and the resulting solution is stirred at 0 °C for 10 min. 4N Aqueous HCl (300 mL) is added, and the aqueous layer is separated and extracted with three 200-mL portions of ethyl acetate. The combined organic layers are washed with 400 mL of saturated aqueous $NaHCO_3$ solution, 400 mL of brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure using a rotary evaporator. The residue is purified by flash column chromatography on 500 g of silica gel (elution with hexane/ethyl acetate, from 7:1 to 3:1). The fractions containing the product are collected and concentrated under reduced pressure using a rotary evaporator to yield 16.77 g (98%) of acetic acid 5-phenylpent-2-ynyl ester (Note 12) as a colorless oil.

D. Acetic acid 2-methylene-3-phenethylbut-3-enyl ester.[3] A flame-dried, 250-mL, two-necked flask equipped with a magnetic stirbar, a rubber septum, and a reflux condenser capped with a three-way stopcock (used as the ethylene inlet adapter) is charged with acetic acid 5-phenylpent-2-ynyl ester (5.16 g, 25.52 mmol) and then 51 mL of anhydrous toluene (Note 13) is added to the flask by syringe. A solution of the second-generation ruthenium carbene complex[4e] (0.217 g, 0.26 mmol, 1 mol %, Note 14) in 5 mL of toluene is then added, and the resulting solution is degassed by repeated freeze-pump-thaw cycles. A 1-gallon (3.8 L) gasbag (Note 15) filled with purified ethylene gas (Notes 16, 17) is connected to the ethylene inlet adapter and the solution is stirred at 80 °C for 2 h under an atmosphere of ethylene gas. After allowing the solution to cool, 6 mL of ethyl vinyl ether is added (Note 18). The solution is concentrated under reduced pressure using a rotary evaporator, and the residue is purified by flash column chromatography on 250 g of silica gel (elution with hexane/ethyl acetate, 7:1). The fractions containing the product are collected and concentrated under reduced pressure using a rotary evaporator to yield 5.68 g (97%) of acetic acid 2-methylene-3-phenethylbut-3-enyl ester (Note 19) as a light yellow oil. Colorless material can be obtained by subjecting this product to Kugelrohr distillation to afford 5.55 g (94%) of the product as a colorless oil (Note 20).

2. Notes

1. Carbon tetrabromide (99%) was purchased from the Aldrich Chemical Company Inc. and was used without further purification.

2. Dichloromethane (unstabilized HPLC grade) was purchased from Fisher Scientific and was dried by percolation through two columns packed with neutral alumina under a positive pressure of argon.

3. Triphenylphosphine (99%) was purchased from the Aldrich Chemical Company Inc. and was used without further purification.

4. 3-Phenylpropionaldehyde (>90%) was purchased from Fluka and was purified by distillation.

5. The product displayed the following properties: R_f 0.73 (10:1 hexane-ether); IR ($CHCl_3$): cm^{-1} 3087, 3066, 3030, 3015, 2928, 2861, 1604, 1496, 1454, 1083, 1030, 907; ^1H NMR (500 MHz, $CDCl_3$): δ 2.42 (q, *J* = 7.7 Hz, 2 H), 2.74 (t, *J* = 7.7 Hz, 2 H), 6.42 (t, *J* = 7.7 Hz, 2 H), 7.19 (br d, *J* = 7.6 Hz, 2 H), 7.22 (br t, *J* = 7.6 Hz, 1 H), 7.31 (br t, *J* = 7.6 Hz, 2 H); ^{13}C NMR (125.7 MHz, $CDCl_3$): δ 33.8, 34.6, 89.5, 126.3, 128.4 (2C), 128.5 (2C), 137.6, 140.6. LRMS EI (relative intensity) *m/z*: 292 (M^++2, 1.0), 290 (M^+, 1.9), 288 (M^+-2, 1.2), 227 (0.9), 225 (1.0), 221 (49), 209 (52), 129 (23), 128 (20), 92 (43), 91 (100), 77 (13). Anal. Calcd for $C_{10}H_{10}$ Br_2: C; 41.42, H; 3.48. Found: C; 41.33, H; 3.40. The spectroscopic data were identical with literature values for material previously prepared by this procedure.[2]

6. Dry HPLC grade tetrahydrofuran was purchased from Fisher and was dried by percolation through two columns packed with neutral alumina under a positive pressure of argon.

7. A hexane solution of *n*-butyllithium was purchased from the Aldrich Chemical Company Inc. and was titrated prior to use.

8. Paraformaldehyde was purchased from Fisher and was used without further purification.

9. 5-Phenylpent-2-yn-1-ol exhibits the following properties: R_f 0.25 (3:1 hexane-ethyl acetate); IR ($CHCl_3$): cm^{-1} 3610 (OH), 3088, 3066, 3029, 3013, 2932, 2874, 2360, 2223, 1604, 1496, 1455, 1430, 1385, 1342, 1233, 1133, 1078, 1006, 968; ^1H NMR (500 MHz, $CDCl_3$): δ 1.60 (t, *J* = 6.0 Hz, 1 H), 2.52 (tt, *J* = 7.5, 2.1 Hz, 2 H), 2.84 (t, *J* = 7.5 Hz, 2 H), 4.23 (dt, *J* = 6.0, 2.1 Hz, 2 H), 7.18-7.26 (m, 3 H), 7.31 (br t, *J* = 7.3 Hz, 2 H); ^{13}C NMR (125.7 MHz, $CDCl_3$): δ 20.9, 34.9, 51.3, 79.0, 85.7, 126.3, 128.38 (2C), 128.40 (2C), 140.5; LRMS EI (relative intensity) *m/z*: 160 (M^+, 1.2), 159 (5), 142 (32), 129 (15), 92 (10), 91 (100), 65 (14). Anal. Calcd for $C_{11}H_{12}O$: C, 82.46; H, 7.55. Found: C, 82.27; H, 7.68.

10. Pyridine (99.9%) was purchased from Fisher and was purified by distillation over CaH_2.

11. Acetic anhydride (99.7%) was purchased from Fisher and was purified by distillation.

12. Acetic acid 5-phenylpent-2-ynyl ester has the following properties: R_f 0.5 (3:1 hexane-ethyl acetate); IR ($CHCl_3$): cm^{-1} 3066, 3028, 2948, 2865, 2237 (alkyne), 1737 (CO), 1604, 1496, 1454, 1438, 1380, 1360, 1224, 1210, 1147, 1078, 1026, 967; ^1H NMR (500 MHz, $CDCl_3$): δ 2.09 (s, 3 H), 2.52 (tt, J = 7.7, 2.1 Hz, 2 H), 2.84 (t, J = 7.7 Hz, 2 H), 4.65 (t, J = 2.1 Hz, 2 H), 7.18-7.24 (m, 3 H), 7.30 (br t, J = 7.1 Hz, 2 H); ^{13}C NMR (125.7 MHz, $CDCl_3$): δ 20.8, 20.9, 34.8, 52.7, 74.7, 86.8, 126.4, 128.4 (4C), 140.4, 170.4; LRMS EI (relative intensity) *m*/*z*: 202 (M^+, 0.14), 201 (0.85), 160 (14), 142 (33), 141 (18), 92 (10), 91 (100), 65 (13). Anal. Calcd for $C_{13}H_{14}O_2$: C, 77.20; H, 6.98. Found: C, 77.37; H, 7.20.

13. Toluene (99.9%) is purchased from Fisher and dried by distillation under argon from sodium benzophenone ketyl.

14. Second-generation ruthenium-carbene complex, (tricyclohexylphosphine-[1,3-bis(2,4,6-trimethylphenyl)-4,5-dihydroimidazol- 2- ylidene] [benzylidene]ruthenium (IV) dichloride),[4e] was purchased from Strem Chemicals.

15. The ethylene gasbag was purchased from the Aldrich Chemical Company, Inc., catalog number Z 18,674-0.

16. Ethylene was purchased from Matheson (>99.5%) and was purified by bubbling it sequentially through an aqueous solution of CuCl (2 g of CuCl in 200 mL of saturated aqueous NH_4Cl), concentrated H_2SO_4, and then a KOH tube as shown in Figure 1. The reaction apparatus for the synthesis of the 1,3-diene is shown in Figure 2.

17. The checkers found that this purification of ethylene was not necessary. Without the purification, the checkers obtained the product quantitatively after purification by chromatography and in 97% yield after distillation. Ethyl vinyl ether is added to quench the reaction.[5]

Figure 1. Purification of Ethylene Gas

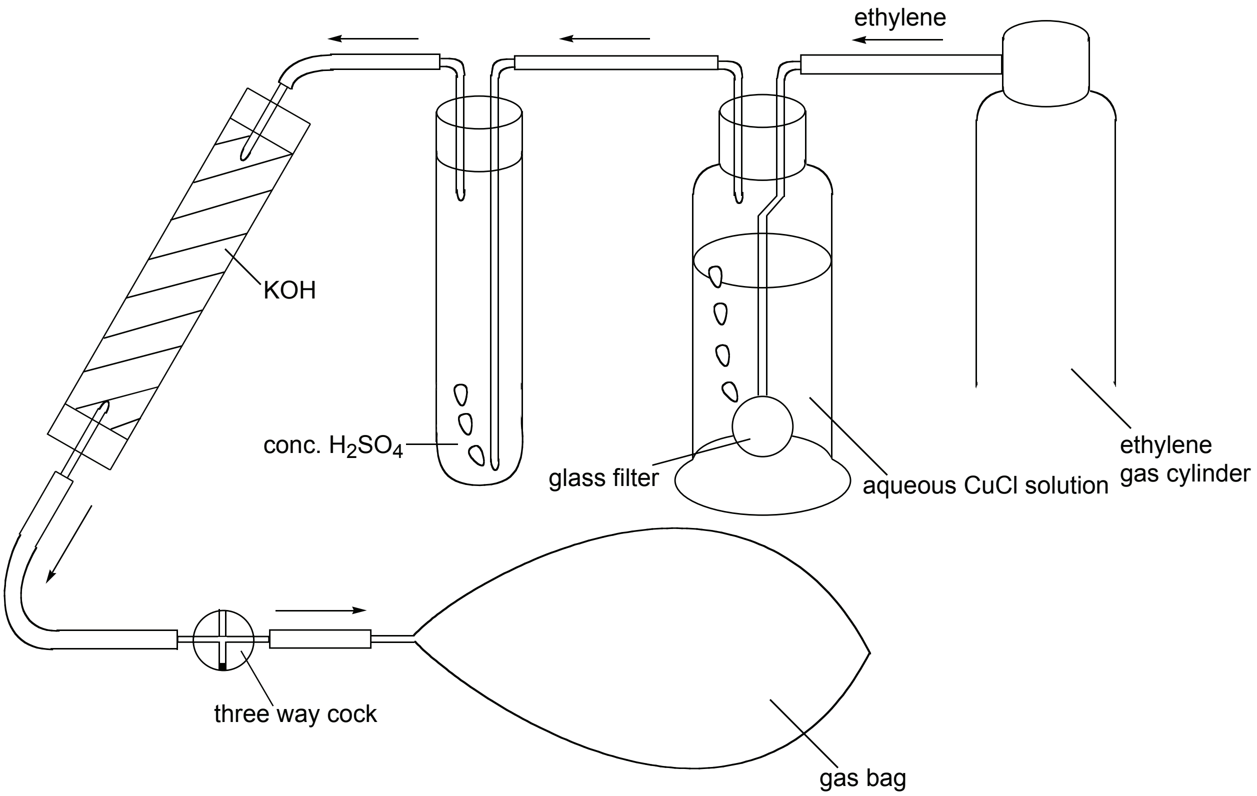
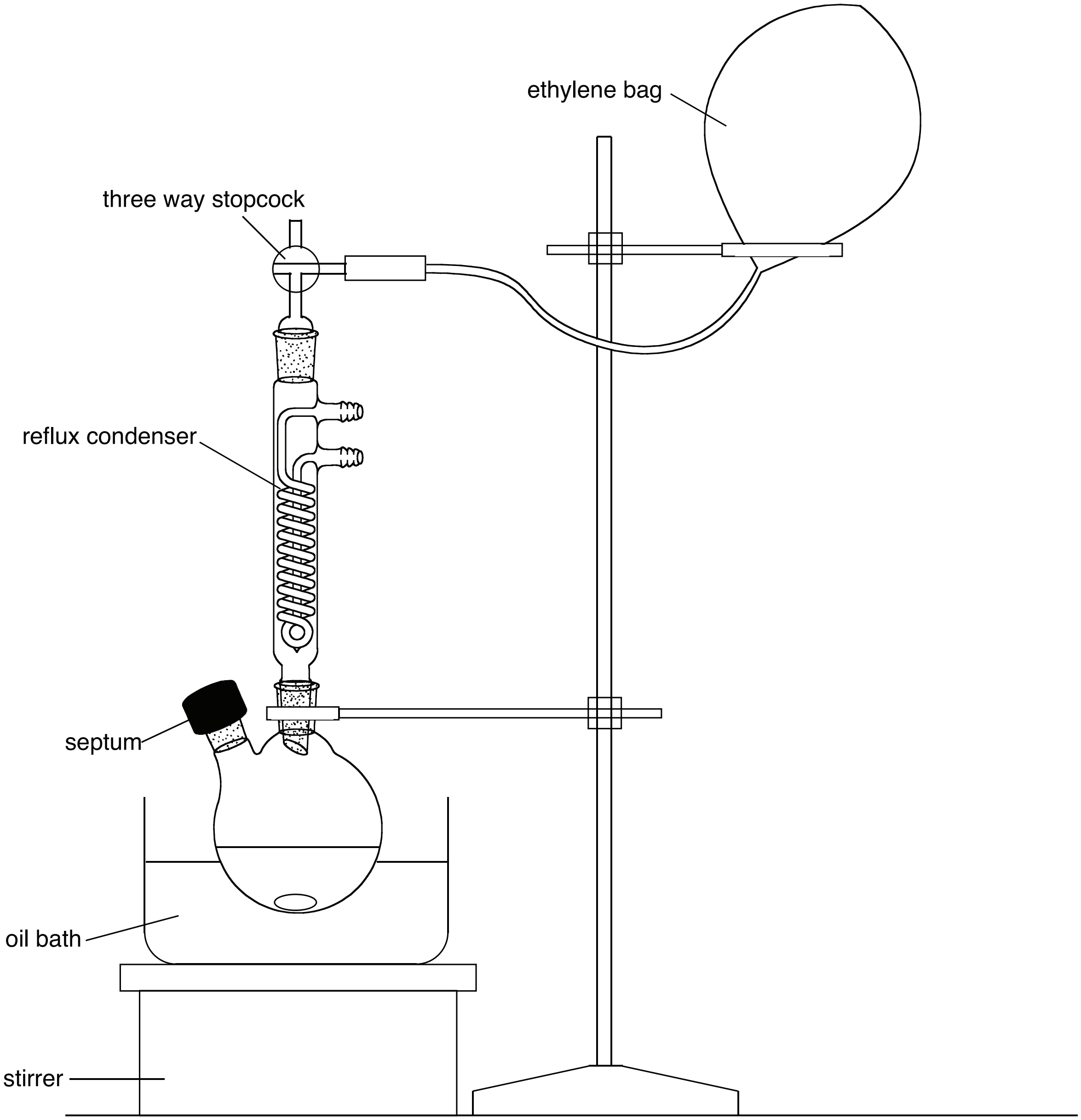


Figure 2. Reaction Apparatus for the Synthesis of 1,3-Diene



18. Ethyl vinyl ether was purchased from the Aldrich Chemical Company Inc. and was used without purification.

19. 2-Methylene-3-phenethylbut-3-enyl acetate has the following properties: R_f 0.55 (3:1 hexane-ethyl acetate); IR ($CHCl_3$): cm^{-1} 3690, 3087, 3065, 3020, 2945, 2865, 2360, 2342, 1736, 1635, 1601, 1496, 1455, 1370, 1222, 1046, 1030, 905; ^{1}H NMR (500 MHz, $CDCl_3$): δ 2.11 (s, 3 H), 2.58 (br t, *J* = 8.1 Hz, 2 H), 2.80 (br t, *J* = 8.1 Hz, 2 H), 4.80 (s, 2 H), 5.03 (br s, 1 H), 5.10 (s, 1 H), 5.31 (br s, 1 H), 5.37 (s, 1 H), 7.16-7.23 (m, 3 H), 7.29 (br t, *J* = 7.3 Hz, 2 H); ^{13}C NMR (125.7 MHz, $CDCl_3$): δ 21.0, 34.7, 35.9, 65.2, 113.1, 114.8, 125.9, 128.34 (2C), 128.38 (2C), 141.4, 141.9, 144.2, 170.8; LRMS EI (relative intensity) *m*/*z*: 230 (M^+, 0.04), 170 (30), 155 (28), 142 (37), 141 (17), 130 (21), 129 (20), 128 (14), 104 (10), 92 (18), 91 (100), 65 (15). Anal. Calcd for $C_{13}H_{18}O_2$: C, 78.23; H, 7.88. Found: C, 78.26; H, 7.91.

20. The checkers found that although the chromatographed product was a light yellow oil, it was analytically pure. Kugelrohr distillation was required to obtain a colorless oil.

Waste Disposal Information

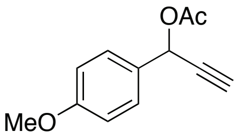
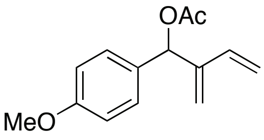
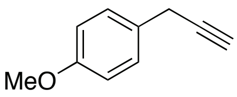
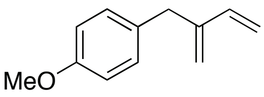
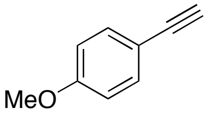
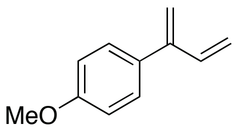
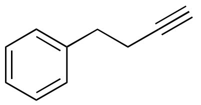
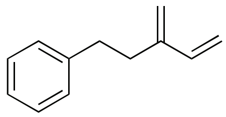
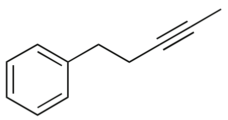
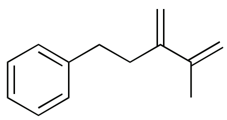
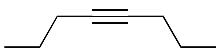
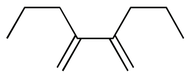
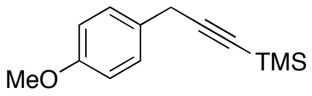
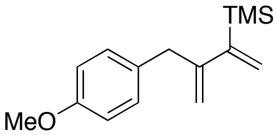
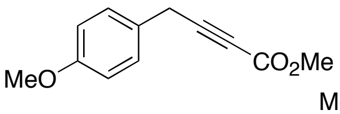
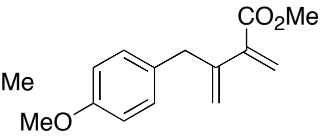
All toxic materials were disposed of in accordance with "Prudent Practices in the Laboratory"; National Academy Press; Washington, DC, 1995.

3. Discussion

This procedure describes the synthesis of 1,3-dienes from alkynes and ethylene (at atmospheric pressure) by ruthenium-catalyzed, cross-enyne metathesis.[3,6] Although this reaction was initially developed using the first-generation ruthenium-carbene complex,[7] the second-generation ruthenium-carbene complex[4] is more effective and the reaction proceeded in the presence of even 1 mol % of the ruthenium catalyst. A number of different functional groups tolerate this reaction. Various 1,3-dienes are obtained in high yields following the procedure described in the text (Table).[3]

1. Graduate School of Pharmaceutical Sciences, Hokkaido University, Sapporo 060-0812, Japan.
2. (a) Renaud, J.-L; Aubert, C.; Malacria, M. *Tetrahedron* **1999**, *55*, 5113. (b) Harada, T.; Katsuhira, T.; Hara, D.; Kotani, Y.; Maejima, K.; Kaji, R.; Oku, A. *J. Org. Chem.* **1993**, *58*, 4897.
3. Tonogaki, K.; Mori, M. *Tetrahedron Lett.* **2002**, *43*, 2235.
4. (a) Weskamp, T.; Schattenmann, W. C.; Spiegler, M.; Herrmann, W. A. *Angew. Chem. Int. Ed.* **1998**, *37*, 2490. (b) Huang, J.; Stevens, E. D.; Nolan, S. P.; Peterson, J. L. *J. Am. Chem. Soc.* **1999**, *121*, 2674. (c) Scholl, M.; Trnka, T. M.; Morgan, J. P.; Grubbs, R. H. *Tetrahedron Lett.* **1999**, *40*, 2247. (d) Jafarpour, L.; Nolan, S. P. *Organometallics* **2000**, *19*, 2055. (e) Scholl, M.; Ding, S.; Lee, C. W.; Grubbs, R. H. *Org. Lett.* **1999**, *1*, 953.
5. Louie, J.; Grubbs, R. H. *Organometallics* **2002**, *21*, 2153.
6. (a) Kinoshita, A.; Sakakibara, N.; Mori, M. *J. Am. Chem. Soc.* **1997**, *119*, 12388. (b) Kinoshita, A.; Sakakibara, N.; Mori, M. *Tetrahedron* **1999**, *55*, 8155. (c) Mori, M.; Tonogaki, K.; Nishiguchi, N. *J. Org. Chem*. **2002**, *67*, 224.
7. Schwab, P.; France, M. B.; Ziller, J. W.; Grubbs, R. H. *Angew. Chem., Int. Ed. Engl.* **1995**, *34,* 2039.

TABLE
SYNTHESIS OF VARIOUS 1,3-DIENES[a]

run	alkyne	diene	time (hr)	yield of diene (%)[b]
1			0.5	100
2			0.5	83
3			0.5	88
4			0.5	71
5			0.5	85
6[c]			24	80
7			16	87 (10)
8[d]			16	43 (34)

a) All reactions were carried out in toluene at 80°C using 5 mol % of ruthenium carbene complex under an atmosphere of ethylene gas by the representative procedure described in the text.
b) The number in parentheses shows the yield of alkyne recovered.
c) This reaction was carried out in CH_2Cl_2 under reflux condition.
d) This reaction was carried out using 10 mol % of ruthenium carbene complex.

Appendix
Chemical Abstracts Nomenclature (Registry Number)

3-Phenylpropionaldehyde: Benzenepropanal; (104-53-0)
(4,4-Dibromobut-3-enyl)benene: Benzene, (4,4-dibromo-3-butenyl)-;
    (119405-97-9)
5-Phenylpent-2-yn-1-ol: 2-Pentyn-1-ol, 5-phenyl-; (16900-77-9)
Acetic acid 5-phenylpent-2-ynyl ester: 2-Pentyn-1-ol, 5-phenyl-, acetate;
    (445234-71-9)
Acetic acid 2-methylene-3-phenethylbut-3-enyl ester: Benzenepentanol,
β,γ-bis(methylene)-, acetate; (445234-76-4)
Carbon tetrabromide: Methane, tetrabromo-; (558-13-4)
Triphenylphosphine: Phosphine, triphenyl-; (603-35-0)
Butyllithium: Lithium, butyl-; (109-72-8)
Paraformaldehyde; (30525-89-4)
Acetic anhydride: Acetic acid, anhydride; (108-24-7)
Pyridine; (108-24-7)
Tricyclohexylphosphine[1,3-bis(2,4,6-trimethylphenyl)-4,5-dihydroimidazol-
    2-ylidene][benzylidene]ruthenium(IV)dichloride: Ruthenium, [1,3-
    bis(2,4,6-trimethylphenyl)-2-
    imidazolidinylidene]dichloro(phenylmethylene)(tricyclohexylphosphine)-,
(SP-5-41)-; (246047-72-3)
Ethyl vinyl ether; Ethene, ethoxy-; (109-92-2)
Ethylene: Ethene; (74-85-1)

```
TK-IX-007-c1f4-7

exp1  s2pul

      SAMPLE            DEC. & VT
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solvent      CDC13  dn              H1
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data/u500/kobayash~ dof              0
i/TK-IX-007-c1f4-7~ dm             nnn
              .fid  dmm              c
   ACQUISITION      dmf            200
sfrq       499.699  dseq
tn              H1  dres           1.0
at           4.665  homo             n
np           65536          DEC2
sw          7024.9  dfrq2            0
fb            4000  dn2
bs               4  dpwr2            1
tpwr            63  dof2             0
pw             5.6  dm2              n
d1               0  dmm2             c
tof            2.0  dmf2           200
nt               4  dseq2
ct               4  dres2          1.0
alock            n  homo2            n
gain      not used       PROCESSING
      FLAGS         wtfile
il               n  proc            ft
in               n  fn        not used
dp               y  math             f
hs              nn
      DISPLAY       werr
sp          -249.9  wexp
wp          5746.3  wbs
vs              35  wnt
sc               0
wc             250
hzmm         22.99
is         1226.28
rfl         4644.3
rfp         3627.8
th               7
ins          2.000
ai    ph
```
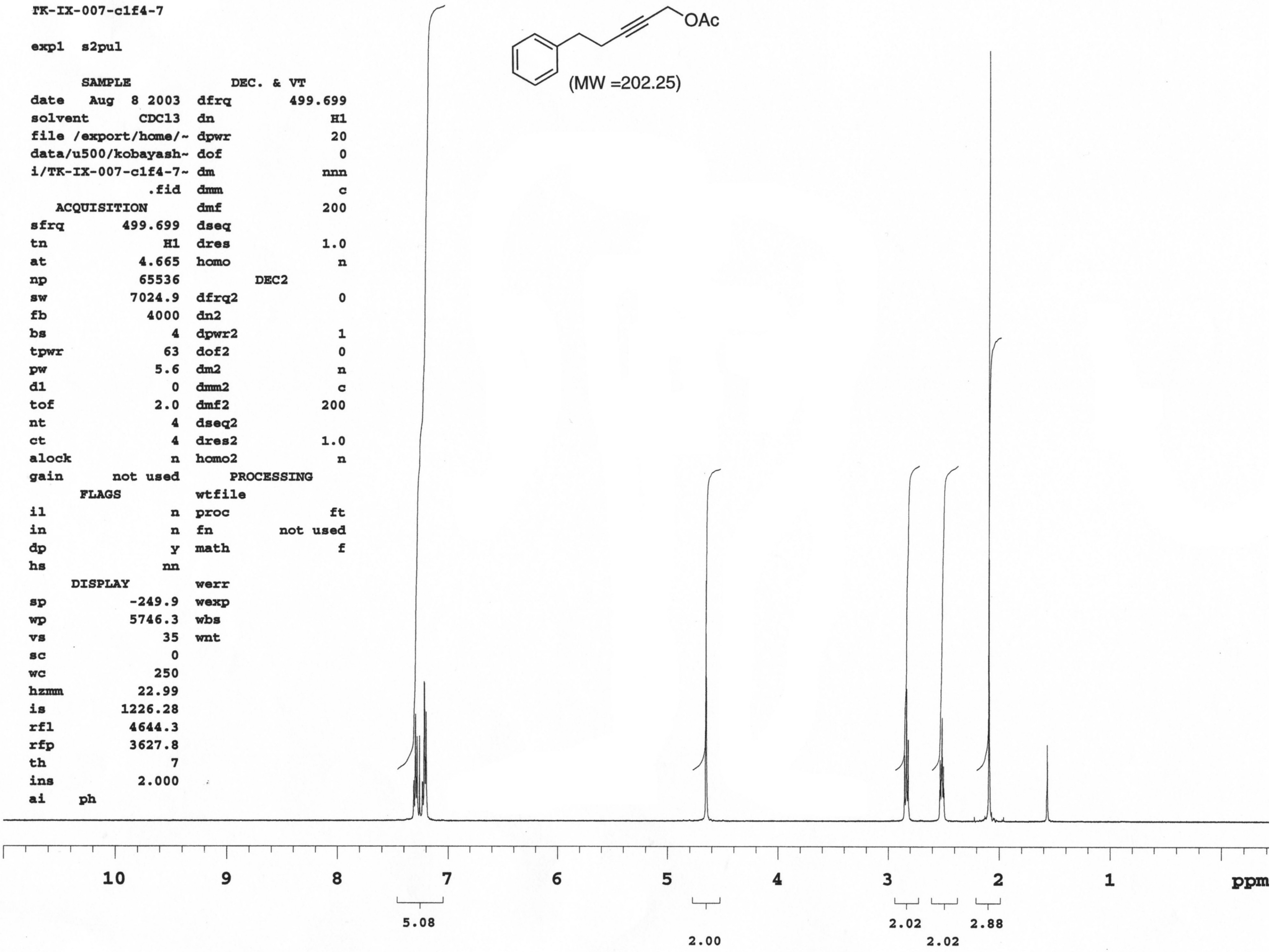
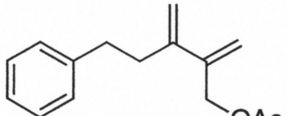

Acetic acid 5-phenylpent-2-ynyl ester



```
TK-IX-011-dist1

exp1  s2pul

      SAMPLE             DEC. & VT
date   Aug 15 2003  dfrq        499.699
solvent      CDCl3  dn               H1
file /export/home/~ dpwr             20
data/u500/kobayash~ dof               0
i/TK-IX-011-dist1.~ dm              nnn
               fid  dmm               c
   ACQUISITION      dmf             200
sfrq       499.699  dseq
tn              H1  dres            1.0
at           4.665  homo              n
np           65536         DEC2
sw          7024.9  dfrq2             0
fb            4000  dn2
bs               4  dpwr2             1
tpwr            63  dof2              0
pw             5.6  dm2               n
d1               0  dmm2              c
tof            2.0  dmf2            200
nt               4  dseq2
ct               4  dres2           1.0
alock            n  homo2             n
gain      not used     PROCESSING
     FLAGS          wtfile
il               n  proc             ft
in               n  fn         not used
dp               y  math              f
hs              nn
    DISPLAY         werr
sp          -249.9  wexp
wp          5746.3  wbs
vs              34  wnt
sc               0
wc             250
hzmm         14.37
is          908.02
rfl         4644.1
rfp         3627.8
th               7
ins          2.000
ai    ph
```

Acetic acid 2-methylene-3-phenethylbut-3-enyl ester



(MW =230.30)