

## PALLADIUM CATALYZED SYNTHESIS OF HETEROCYCLES

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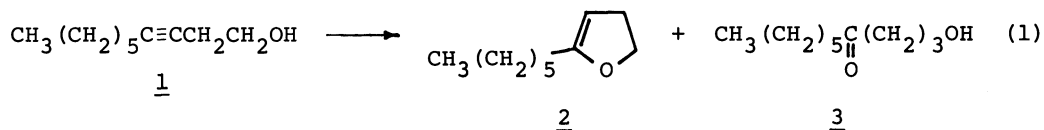
**Abstract** - Novel procedures of constructing heterocycles are described which employ palladium catalyzed intramolecular addition of amino or hydroxyl group to an acetylene bond as a key reaction. Pyrroles and furans are prepared from 1-amino-3-alkyn-2-ols and 3-alkyne-1,2-diols, respectively. Successive addition of two hydroxyl groups to one acetylene bond gives various types of acetals. Insect pheromones containing intramolecular acetal linkage are produced by applying this reaction.

### INTRODUCTION

Hydration of unactivated acetylenes to form ketones has found considerable synthetic use (Ref. 1). Terminal acetylenes almost invariably yield methyl ketones. Regioselective hydration of internal acetylenes stems from anchimeric assistance (Ref. 2,3) and intramolecular reaction of hydroxyl group to acetylene bond plays a key role to synthesize prostacyclin (Ref. 3,4). The above described reactions are usually catalyzed by mercuric salts. Intramolecular addition of protic group such as amino and hydroxyl to carbon carbon triple bond seems to be promising to construct various kinds of heterocycles. Studies on the subject utilizing palladium catalyst are described in this paper.

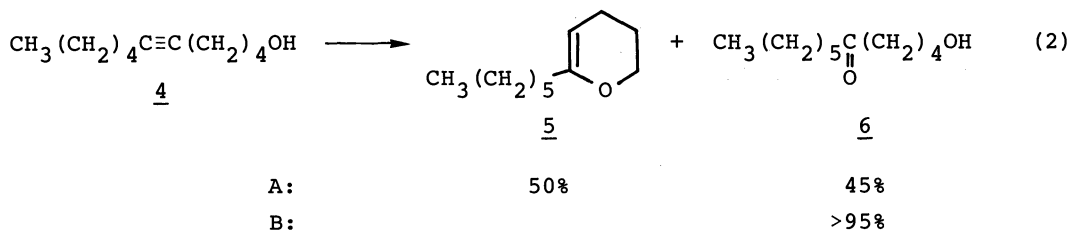
### INTRAMOLECULAR ADDITION OF HYDROXYL OR AMINO GROUP TO ACETYLENES

Palladium(II) species have been found to be effective to the intramolecular addition of hydroxyl across acetylenes. Regioselectivity of the reactions is illustrated by the cases of 3-, 4-, and 5-alkyn-1-ols. Reactions are carried out in anhydrous ether utilizing  $\text{PdCl}_2(\text{PhCN})_2$  as catalyst (condition A) or in aqueous acetonitrile utilizing  $\text{PdCl}_2$  as catalyst (condition B). Under condition A, 3-decyn-1-ol cyclizes in 5-Endo-Dig manner giving dihydrofuran 2 as a predominant product. Reaction under condition B gives exclusively hydroxy ketone 3 which is the hydrolyzed product of 2.

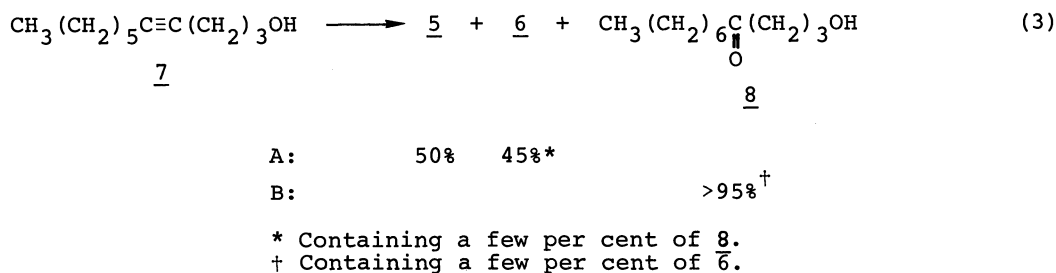


|  |     |      |
|--|-----|------|
| A: $\text{PdCl}_2(\text{PhCN})_2$ (0.01-0.03 equiv.) |     |      |
| anhydrous $\text{Et}_2\text{O}$ , r.t., 5-10 h       | 60% | 30%  |
| B: $\text{PdCl}_2$ (0.01-0.05 equiv.)                |     |      |
| aqueous $\text{CH}_3\text{CN}$ , reflux 30 min.      |     | >95% |

5-Undecen-1-ol cyclizes in 6-Exo-Dig manner and gives dihydropyran 5 and its hydrolyzed hydroxy ketone 6.

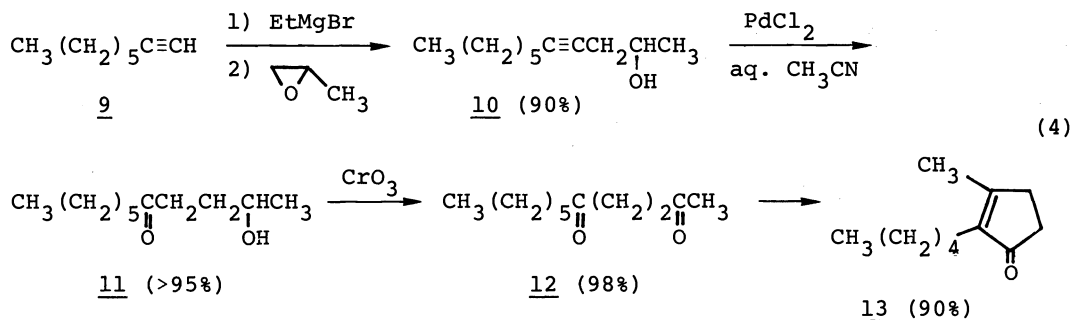


In contrast to the above reactions, 4-undecyn-1-ol predominantly cyclizes in 6-Endo-Dig manner under condition A, whereas 5-Exo-Dig cyclization is preferable under condition B giving 1-hydroxy-4-undecanone as the major product.

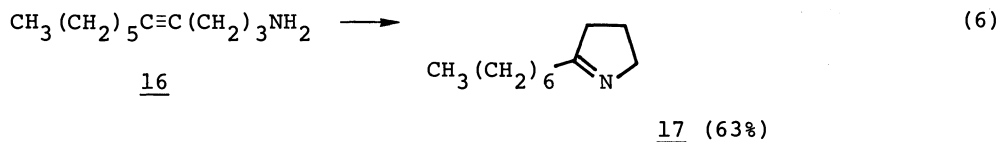
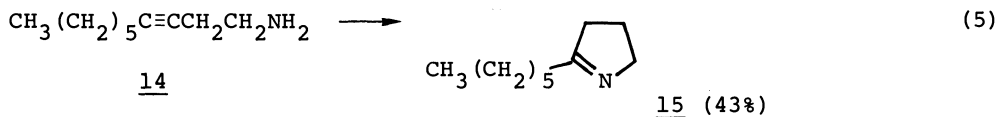


Results shown in eq. 1-3 suggest that dihydrofuran and dihydropyran derivatives are easily prepared from 3-alkyn-1-ols and 5-alkyn-1-ols, respectively, by the catalytic action of  $\text{PdCl}_2(\text{PhCN})_2$  in ether (condition A). Easy access to 1,4-dicarbonyl compounds from 3-alkyn-1-ols or 4-alkyn-1-ols and 1,5-dicarbonyl derivatives from 4-alkyn-1-ols or 5-alkyn-1-ols is also suggested.

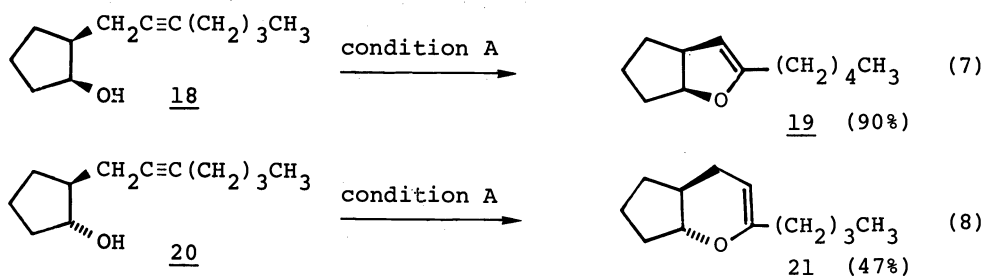
Preparation of dihydrojasnone from the corresponding alkynol is illustrative of the utility (eq. 4).



Amino group also adds to acetylene bond intramolecularly by the catalytic action of  $\text{PdCl}_2$  in refluxing acetonitrile. Examples are shown in eq. 5-6.

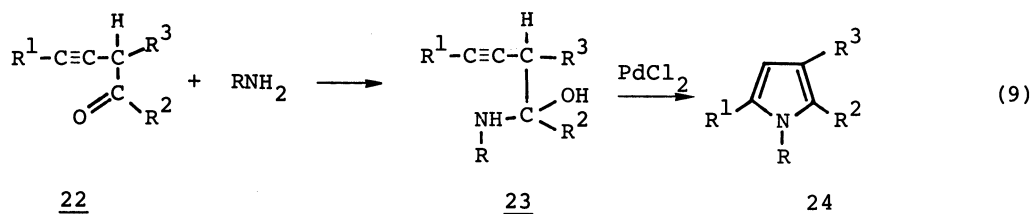


The above described reaction is applied to cyclic systems. Orientation of the addition depends upon the stereochemistry of the starting material. Two examples of intramolecular addition of alcohol to acetylene are illustrative (eq. 7,8). Riediker and Schwartz have reported similar results (Ref. 3).

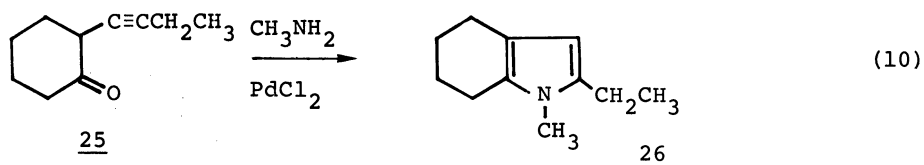


## SYNTHESIS OF PYRROLES AND FURANS

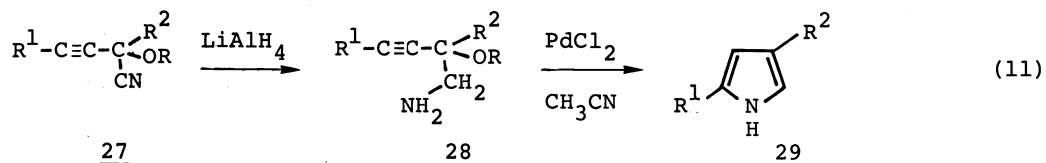
**Pyrrroles.** Pyrrole ring can be constructed by the application of the above described intramolecular addition of amino group to acetylene bond. One general scheme is presented as follows:



Reaction of 4-undecyn-2-one (22, R<sup>1</sup> = CH<sub>3</sub>(CH<sub>2</sub>)<sub>5</sub>, R<sup>2</sup> = CH<sub>3</sub>, R<sup>3</sup> = H) and methylamine under the catalytic action of PdCl<sub>2</sub> gives pyrrole 24 (R<sup>1</sup> = CH<sub>3</sub>(CH<sub>2</sub>)<sub>5</sub>, R<sup>2</sup> = CH<sub>3</sub>, R<sup>3</sup> = H, R = CH<sub>3</sub>) in 50% yield. 2-(1-Butynyl)cyclohexan-1-one affords 26 in 30% yield (eq. 10).



Equation 11 presents another synthetic reaction of pyrroles.



Starting material 27 (R = CH<sub>3</sub>) can be prepared from the corresponding acetal (27, R = CH<sub>3</sub>, R<sup>2</sup> = OCH<sub>3</sub>) by the treatment with cyanotrimethylsilane (Ref. 5). Compound 27 (R = SiMe<sub>3</sub>) is obtained from acetylenic ketone by the reaction with cyanotrimethylsilane.

Conversion of 28 to 29 is effectively catalyzed by PdCl<sub>2</sub>. Palladium acetate, in place of PdCl<sub>2</sub>, gives a similar result but Pd(Ph<sub>3</sub>P)<sub>4</sub> is less effective. Pyrroles prepared by eq. 11 are shown in Table 1.

TABLE 1. Pyrrole 29 prepared from 28<sup>a</sup>

| Entry | Starting material <u>28</u>                     |                                   |                 | Catalyst (equiv.)                         | Yield of <u>29</u> (%) <sup>b</sup> |
|-------|---|-----------------------------------|-----------------|---|-------------------------------------|
|       | R <sup>1</sup>                                  | R <sup>2</sup>                    | R               |   |                                     |
| 1     | CH <sub>3</sub> (CH <sub>2</sub> ) <sub>5</sub> | CH <sub>3</sub> CH <sub>2</sub>   | H               | PdCl <sub>2</sub> (0.01)                  | 84                                  |
| 2     | "   | "                                 | "               | PdCl <sub>2</sub> (0.001)                 | 83                                  |
| 3     | "   | "                                 | "               | Pd(OAc) <sub>2</sub> (0.01)               | 73 <sup>c</sup>                     |
| 4     | "   | "                                 | "               | Pd(PPh <sub>3</sub> ) <sub>4</sub> (0.01) | 17 <sup>d</sup>                     |
| 5     | "   | (CH <sub>3</sub> ) <sub>3</sub> C | "               | PdCl <sub>2</sub> (0.01)                  | 85                                  |
| 6     | "   | "                                 | CH <sub>3</sub> | PdCl <sub>2</sub> (0.01)                  | 88                                  |
| 7     | Ph  | CH <sub>3</sub> CH <sub>2</sub>   | H               | PdCl <sub>2</sub> (0.01)                  | >99                                 |
| 8     | (CH <sub>3</sub> ) <sub>3</sub> Si              | CH <sub>3</sub> CH <sub>2</sub>   | H               | PdCl <sub>2</sub> (0.01)                  | 28 <sup>e</sup>                     |

- a) Reaction was carried out in refluxing acetonitrile for 3 h.  
 b) Glc yields are quantitative except entries 3, 4 and 8.  
 c) The yield diminished to 70% when benzene was employed as solvent.  
 d) Air was introduced to an acetonitrile solution of catalyst, yield increased to 70%.  
 e) The obtained product was 29 (R<sup>1</sup> = H, R<sup>2</sup> = CH<sub>3</sub>CH<sub>2</sub>).

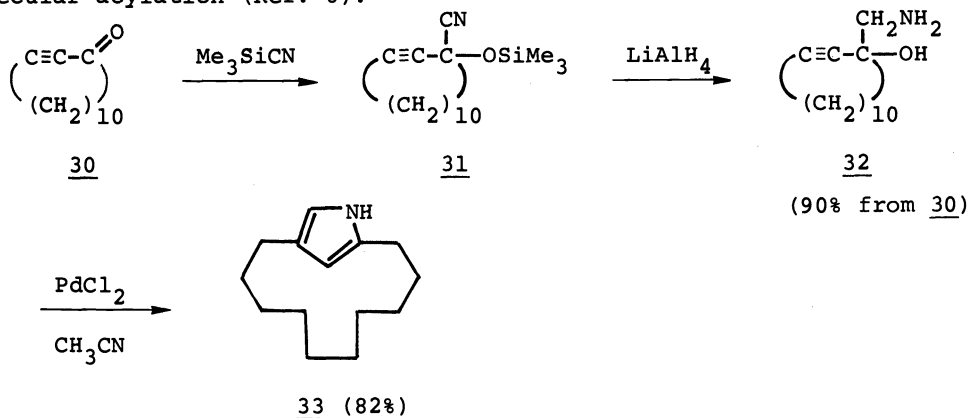
Cyclization using various different metal salts as catalysts was examined. Results are given in Table 2.

TABLE 2. Synthesis of 4-ethyl-2-hexylpyrrole<sup>a</sup>

| Catalyst  | Yield (%) | Catalyst                             | Yield (%) |
|---|-----------|--------------------------------------|-----------|
| PdCl <sub>2</sub>                                   | 84        | RhCl <sub>3</sub> ·3H <sub>2</sub> O | 57        |
| H <sub>2</sub> PtCl <sub>6</sub> ·6H <sub>2</sub> O | 70        | NiCl <sub>2</sub>                    | 28        |
| AgOCOCH <sub>3</sub>                                | 67        | SnCl <sub>4</sub>                    | 23        |
| CuCl  | 62        | AlCl <sub>3</sub>                    | 11        |

- a) Used 0.01 equiv. of metal salt as catalyst and heated to reflux for 3-5 h in acetonitrile.

The above new method is applied to the synthesis of pyrrolophanes. An example is shown in eq. 12. 2-Cyclotridecyn-1-one is easily prepared by intramolecular acylation (Ref. 6).



(12)

**Furans.** Analogous to the above described pyrrole synthesis, furans are prepared from  $\beta,\gamma$ -acetylenic ketones (eq. 13) or 2-methoxy-3-alkyn-1-ols (eq. 14). Combinations of the starting material, reaction conditions, and the yield of furan 35 are summarized in Table 3.

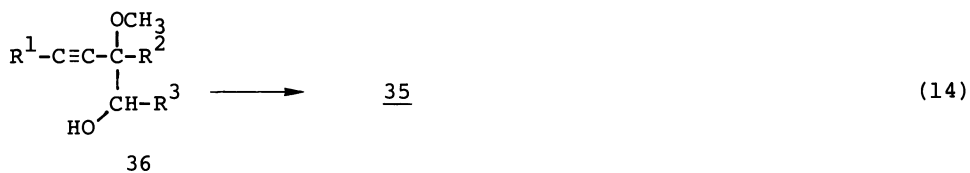
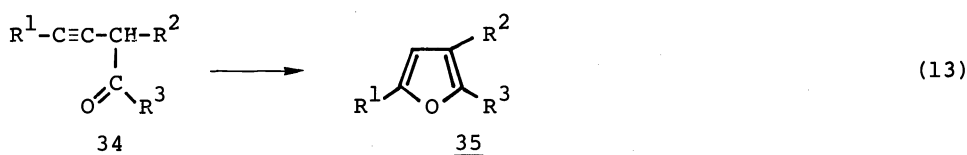


TABLE 3. Synthesis of furan 35

| Entry | Starting material | R <sup>1</sup>                                  | R <sup>2</sup>                     | R <sup>3</sup>  | Condition <sup>a</sup> | <u>35</u> Yield (%) |
|-------|-------------------|---|------------------------------------|-----------------|------------------------|---------------------|
| 1     | <u>34</u>         | CH <sub>3</sub> CH <sub>2</sub>                 | -(CH <sub>2</sub> ) <sub>4</sub> - |                 | D                      | 60                  |
| 2     | <u>34</u>         | CH <sub>3</sub> (CH <sub>2</sub> ) <sub>5</sub> | H                                  | CH <sub>3</sub> | D                      | 75                  |
| 3     | <u>36</u>         | "   | CH <sub>3</sub>                    | H               | E                      | 80                  |
| 4     | <u>36</u>         | "   | "                                  | "               | F                      | 24                  |
| 5     | <u>36</u>         | "   | "                                  | CH <sub>3</sub> | E                      | 94                  |
| 6     | <u>36</u>         | "   | "                                  | "               | F                      | 27                  |
| 7     | <u>36</u>         | "   | "                                  | "               | G                      | 94                  |
| 8     | <u>36</u>         | "   | H                                  | H               | E <sup>b</sup>         | 90                  |
| 9     | <u>36</u>         | "   | "                                  | "               | E                      | 0                   |

a) Condition D: PdCl<sub>2</sub> (0.05 equiv.) in aq. CH<sub>3</sub>CN, reflux 3 h.

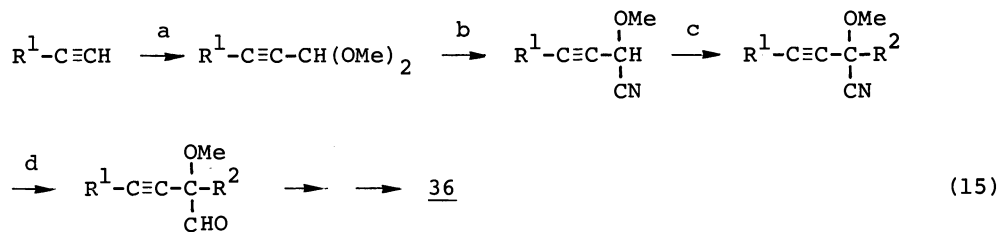
E: PdCl<sub>2</sub>(PhCN)<sub>2</sub> (0.05) in aq. THF, r.t., 5 h.

F: PdCl<sub>2</sub> (0.05) in anhydrous CH<sub>3</sub>CN, reflux 10 h.

G: PdCl<sub>2</sub> (0.05) in aq. CH<sub>3</sub>CN, r.t., 5 h.

b) Reaction in THF-dil. HCl, r.t., 24 h.

Starting material 36 can be prepared in excellent overall yield from simple building blocks such as 1-alkynes, orthoformate, and cyanotrimethylsilane (eq. 15).



a: EtMgBr, HC(OMe)<sub>3</sub>

c: LDA, R<sup>2</sup>I

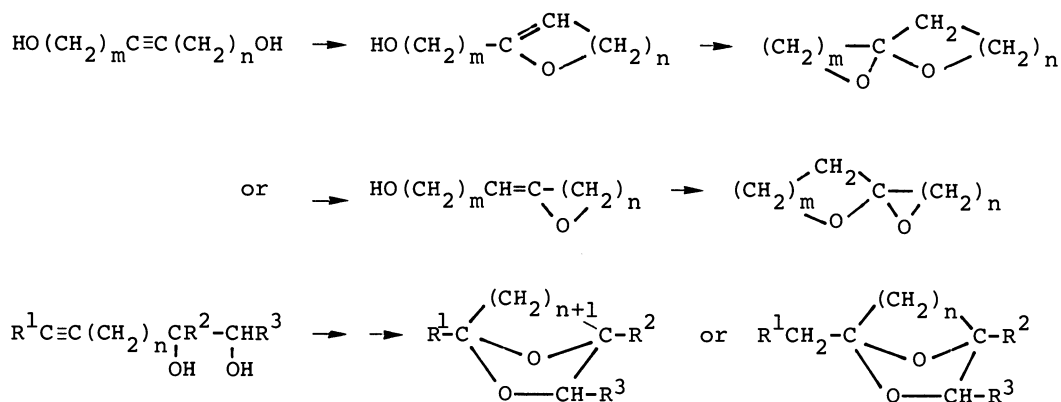
b: Me<sub>3</sub>SiCN-BF<sub>3</sub>·OEt<sub>2</sub>

d: <sup>i</sup>Bu<sub>2</sub>AlH

## SYNTHESIS OF PHEROMONES WITH INTRAMOLECULAR ACETAL LINKAGE

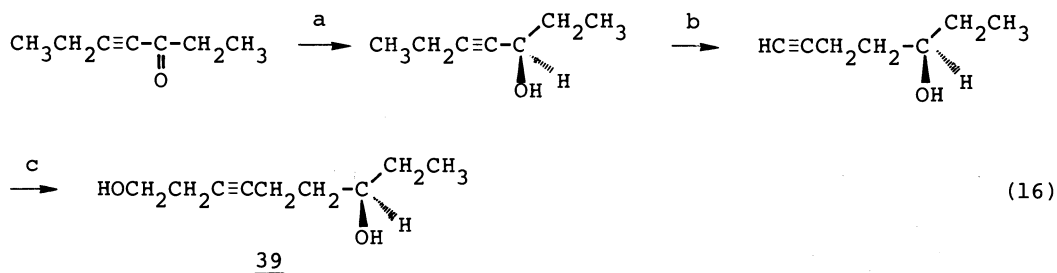
Intramolecular addition of hydroxyl group to an acetylene bond suggests that intramolecular acetals could be prepared from acetylenes containing two hydroxyl groups at appropriate positions by successive addition of two hydroxyl groups to one acetylene bond. The observation that alcohols add to dihydropyran under the catalytic action of  $\text{PdCl}_2(\text{PhCN})_2$  affording dihydropyranyl ethers (Ref. 7) indicates the reactions shown in scheme 1 is promising.

SCHEME 1



As the target molecules are chosen pheromones with intramolecular acetal linkage which have been prepared from dihydroxy ketones (Ref. 8,9). Pheromones with spiroacetal linkage are prepared from alkynediols as shown in table 4.

Spiroacetal 44 is the principal aggregation pheromone of *Pityogenes chalcographus* (L.), a bark-beetle named "Kupferstecher" (Ref. 10). Optically active (7R)-3-nonyne-1,7-diol (39) is prepared from 4-heptyn-3-one by successive transformations shown in eq. 16.



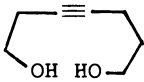
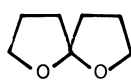
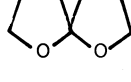
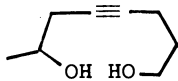
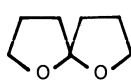
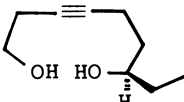
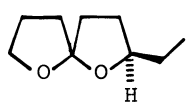
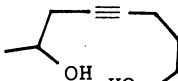
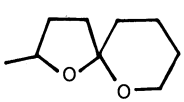
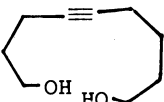
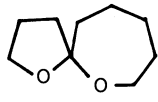
a:  $\text{LiAlH}_4$ - (2S,3R)-(+)-4-dimethylamino-1,2-diphenyl-3-methyl-2-butanol (Ref. 11).

b:  $\text{KNHCH}_2\text{CH}_2\text{CH}_2\text{NH}_2$  (Ref. 12, 13).

c: dihydropyran,  $\text{H}^+$ ;  $\text{EtMgBr}$ ; oxirane;  $\text{H}_2\text{O}$ ,  $\text{H}^+$ .

As can be seen from eq. 16, acetylene walk from internal to terminal is a powerful tool to construct acetylenes shown in table 4. Additionally chiral center is not touched during the reaction (Ref. 13) and the procedure can be applied to chiral compounds without trouble.

TABLE 4. Synthesis of spiroacetals from alkyne diols

| Entry | Alkyne diol   | Condition <sup>a</sup> | Spiroacetal (Yield %)   |
|-------|---|------------------------|---|
| 1     |  | A                      |  (90) |
|       |   | G                      |  (95) |
| 2     |  | A                      |  (85) |
| 3     |  | G                      |  (95) |
| 4     |  | G                      |  (85) |
| 5     |  | G                      |  (60) |

a) Condition A: PdCl<sub>2</sub>(PhCN)<sub>2</sub> (0.01 equiv.) in ether, r.t., 5 h.

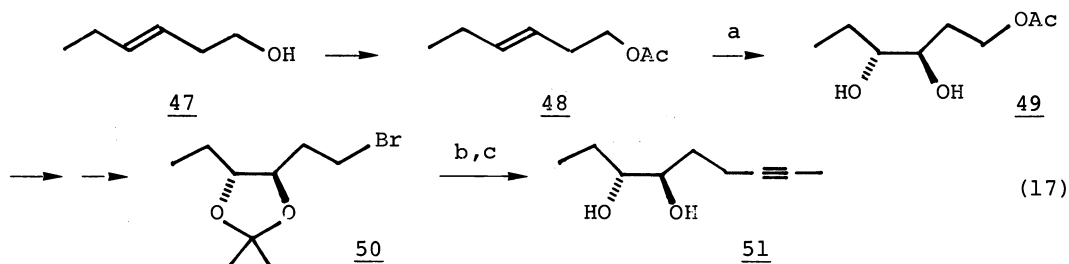
G: PdCl<sub>2</sub> (0.01 equiv.) in aq. CH<sub>3</sub>CN, reflux, 1 h.

b) Mixture of two diastereomers (1:1).

c) Pheromone isolated from *Dolichovespula saxonica*, *Paravespula germanica*, and *Paravespula vulgaris*.

d) 2,7-Dioxaspiro[5.5]undecane could not be detected.

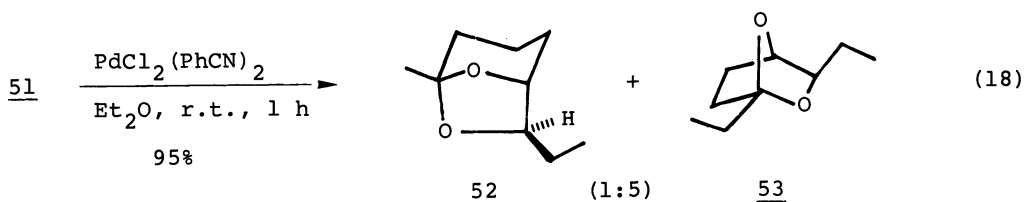
Pheromones with bicyclic acetal linkage are the next target molecules. *exo*-Brevicomín, the principal aggregation pheromone of the western pine beetle (*Dendroctonus brevicomis*), and frontalin, aggregation pheromone of southern pine beetle (*Dendroctonus frontalis*), are synthesized. Starting from (*E*)-3-hexen-1-ol, threo-7-nonyne-3,4-diol is prepared and treated with palladium catalyst in ether affording a mixture of two acetals (eq. 17, 18).



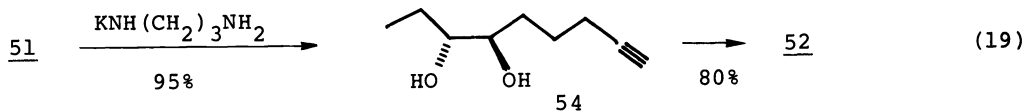
a: KMnO<sub>4</sub>

b: CH<sub>3</sub>C≡CLi/THF-HMPT

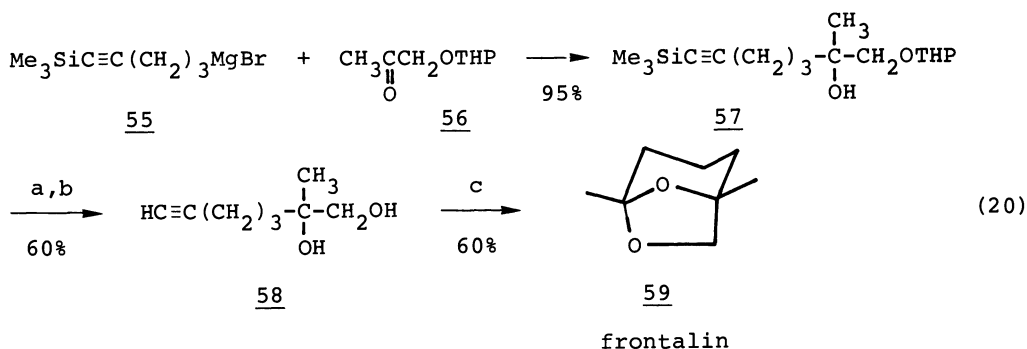
c: MeOH, p-CH<sub>3</sub>C<sub>6</sub>H<sub>4</sub>SO<sub>3</sub>H



Migration of internal triple bond in 51 to the terminal position affords 54 in 95% yield. Palladium catalyzed cyclization of 54 gives exo-brevicomin exclusively (eq. 19).



Analogous to the synthesis of exo-brevicomin shown in eq. 19, frontalin can be prepared (eq. 20).



a: KF in DMSO    b: MeOH, p-CH<sub>3</sub>C<sub>6</sub>H<sub>4</sub>SO<sub>3</sub>H  
 c: PdCl<sub>2</sub>(PhCN)<sub>2</sub> (0.01 equiv.) in THF, r.t., 24 h

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