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Synthesis of Seven-Membered Carbocyclic Rings via a Microwave-Assisted Tandem Oxyanionic 5-Exo Dig Cyclization-Claisen Rearrangement Process

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Abstract

Appropriately substituted 1-alkenyl-4-pentyn-1-ol systems, readily prepared from simple starting materials, serve as useful precursors to a number of substituted cyclohept-4-enone derivatives via a microwave-assisted tandem oxyanionic 5-exo cyclization/Claisen rearrangement sequence. The reactions involving terminally substituted 4-pentyn-1-ols were found to be highly stereoselective, with the α and β groups in the final product showing a strong preference for the *trans* orientation.

Carbocyclic seven-membered rings are common structural units that can be found in a variety of polycyclic natural products many of which are of considerable medicinal interest. Among them are the phorbol esters,¹ guanacastepenes,² guianolides³ as well as the frondosins.⁴ Unlike smaller ring sizes -especially five and six-membered rings- which are readily accessible through various cyclization reactions, the construction of seven-membered rings is more challenging and generally limited to processes other than direct intramolecular reactions. Among the most important of these are various cycloaddition strategies, such as the [5+2] and [4+3] reactions, which have proved useful for effecting the synthesis of a number of cycloheptanoid natural products.⁵

An alternative approach to carbocyclic seven-membered rings takes advantage of the Claisen rearrangement reaction of appropriately substituted exocyclic 2-alkylidene-tetrahydrofuran derivatives; however, the synthetic utility this process is severely limited by the accessibility of the requisite allyl vinyl ether precursors.⁶ Consequently, the exploitation of this strategy for the synthesis polycyclic cycloheptanoid ring structures of the type shown in Figure 1 has not been widely utilized, most likely due to difficulties associated with the preparation of the requisite starting materials.

We have recently demonstrated that a variety of cycloheptanoid fused ring systems may be conveniently accessed through a known⁷ but largely ignored tandem sequence that involves a base-catalyzed intramolecular cyclization of appropriately substituted tertiary acetylenic alcohols (4-pentyn-1-ols), followed by in situ Claisen rearrangement of the intermediate 2-alkylidenetetrahydrofurans.⁸ The requisite allyl vinyl ether precursor in these reactions is produced as a transient species through a 5-exo dig process involving the intramolecular addition of an alkoxide moiety to a proximal triple bond. Under high-temperature conditions -most conveniently achieved using microwave irradiation- this intermediate rearranges directly to afford a cyclohept-4-enone derivative via the [3,3] sigmatropic process. It is noteworthy that although the generation of various furanyl systems by transition metal catalyzed 5-exo dig

cyclizations of acetylenic alcohols has been amply documented,⁹ the formation of 2-alkylidenetetrahydrofurans by intramolecular addition of an alkoxide moiety to triple bonds is much less common.

Investigations conducted in our laboratory to date have involved tertiary acetylenic alcohols, which seem particularly well suited as precursors for the cyclization/Claisen sequence. In this note, we wish to report a useful and practical extension of this methodology, which takes advantage of secondary 4-pentyn-1-ol systems as precursors a variety of substituted seven-membered ring containing compounds, particularly mono- and bicyclic $\alpha\beta$ -disubstituted 4-cycloheptenone derivatives according to the general strategy depicted in Scheme 1.

The 4-pentyn-1-ol derivatives used for this study were easily prepared from readily available starting materials in just a few simple steps. A representative example is shown in Scheme 2. Thus, commercially available 4-pentyn-1-ol was arylated with 1-bromo-2,5-dimethoxy benzene according to the Sonogashira protocol¹⁰ to give a known¹¹ alcohol product, which was subsequently subjected to Swern oxidation.¹² The resulting aldehyde **1** was then reacted with cyclopentenyl lithium, prepared in situ from the corresponding vinyl iodide by low-temperature lithium-halogen exchange reaction, to afford the desired Claisen precursor **2** in 67% yield over three steps. On exposure to catalytic MeLi (ca. 10 mol-%) and microwave irradiation, **2** was smoothly converted to the α -arylated bicyclo[5.3.0]decane system **3** as a 93:7 mixture of diastereomers in 76% isolated yield.

The cyclization/Claisen rearrangement sequence involving 5-aryl substituted 4-pentyn-1-ols such as **2** is significant considering that the synthetically equivalent regioselective α -arylation reaction of analogous hydroazuleneone systems is difficult to achieve using existing methodology. In general, palladium-catalyzed α -arylation reactions have not been widely applied for the synthesis of highly substituted cycloheptanone derivatives.¹³

The tandem process also works well with alcohols bearing terminal triple bonds (Table 1, entries 2 and 5) and even alkyl substituted secondary alcohols react provided that the initial ring closure is facilitated through operation of the Thorpe-Ingold effect.¹⁴ Indeed, while simple alkyl substituted acetylenic alcohols were unreactive under the conditions investigated, the secondary alcohol **22** bearing a gem-dimethyl moiety in the flexible alkyl tether connecting to the alkyne unit gave the expected bicyclic ring system **23** in 60% yield (Table 1, entry 11). The carbomethoxy derivative **20** also cyclized readily to afford the known tetrahydrofuran system **21** exclusively as the corresponding *E*-isomer; however, no formation of the rearranged product was observed under these conditions (Table 1, entry 10).¹⁵

The reaction involving enyne **10** also provided the expected bicyclo[5.4.0]undecane ring system; however, the Claisen rearrangement in this case was accompanied by isomerization of product (Table 1, entry 4). Results from these and other experiments are summarized in Table 1.

Reactions involving terminally substituted 4-pentyn-1-ols were found to be highly stereoselective, with R¹ and R² groups (Scheme 1) showing a strong preference for *trans* orientation in the final product. The observed stereochemical trends in these processes may be justified by invoking a chair-like transition state for the Claisen rearrangement and considering steric interactions within the transition state structures **15a** and **15b** (Scheme 3). It is reasonable to assume that the transition state in which the phenyl group occupies a pseudo equatorial orientation (**15a**) is more favorable than that involving a pseudo axial phenyl group (**15b**).

Consistent with earlier reports regarding the configurational lability of vinyl anions bearing aryl substituents,¹⁶ the Claisen precursors **14a** and **14b** may be derived from isomerization of the vinyl anion intermediates formed upon the initial base-catalyzed 5-exo cyclization reaction

involving **14**. It is also possible that neutral enol ethers **14a** and **14b** exist in equilibrium under the high-temperature conditions employed and interconvert via an endo-exo isomerization process,^{6,7, 8h} thereby serving as precursors to either of the two transition state structures **15a** and **15b**.

We have previously reported that the initial diastereomer ratio of products obtained via the cyclization-Claisen rearrangement processes could be significantly altered upon treatment with alkoxide bases and heat (e.g. from 2.5:1 to 14.6:1).^{8g,h} The same trend was observed here. In the specific case examined, a 77:23 mixture of **17/17a**, obtained directly from the cyclization-Claisen rearrangement process, was subjected to NaOMe/MeOH at reflux (65 °C). Analysis of the reaction mixture after 15h of heating revealed an 88:12 ratio of **17/17a** (Scheme 4), representing a notable change from the initial product distribution. The same ratio was obtained when a chromatographically enriched 92:8 mixture of the diastereomers was subjected to identical conditions.¹⁷

In conclusion, we have shown that appropriately substituted 1-alkenyl-4-pentyn-1-ol systems, readily prepared from simple starting materials, serve as useful precursors to a number of substituted cyclohept-4-enone derivatives via a microwave-assisted tandem oxyanionic 5-exo cyclization/Claisen rearrangement sequence.

Experimental Section

General Procedure for the Preparation of 4-Alkyn-1-ol Derivatives: Preparation of 1-Cyclopentenyl-5-(2,5-dimethoxyphenyl)pent-4-yn-1-ol (**2**)

To a -78 °C solution of 1-iodocyclopentene (776 mg, 4.00 mmol) in 15 mL Et₂O was added *t*-BuLi (1.7 M in pentane, 4.7 mL, 8.0 mmol) dropwise. The resulting solution was stirred at -78 °C for 15 min, then warmed to 0 °C and stirred for another 15 min at this temperature to destroy any excess *t*-BuLi. After re-cooling to -78 °C, aldehyde **1** (436 mg, 2.00 mmol) in Et₂O (15 mL) was added dropwise to the solution. The resulting mixture was stirred thereafter for 20 min and then quenched by the addition of aqueous NH₄Cl. The layers were separated and the aqueous layer was extracted with Et₂O. The combined organic extracts were washed with brine, dried over MgSO₄, filtered, and concentrated under reduced pressure. The crude product was purified by column chromatography (20% EtOAc in hexane) to give alcohol **2** as a pale yellow oil (509 mg, 89%). IR (neat) 3446, 2927, 1605, 1495, 1049, 824 cm⁻¹; ¹H NMR (CDCl₃, 500 MHz) δ 6.89 (d, *J* = 3.0 Hz, 1 H), 6.76-6.72 (m, 2 H), 5.63 (d, *J* = 1.5 Hz, 1 H), 4.45 (dd, *J* = 6.0, 4.5 Hz, 1 H), 3.79 (s, 3 H), 3.71 (s, 3 H), 2.58-2.46 (m, 2 H), 2.44 (br s, 1 H), 2.32-2.27 (m, 4 H), 1.92-1.80 (m, 4 H); ¹³C NMR (CDCl₃, 125 MHz) δ 154.2, 153.0, 146.3, 125.4, 118.0, 114.6, 113.2, 111.6, 93.9, 77.1, 70.2, 56.1, 55.5, 34.1, 32.1, 31.2, 23.2, 16.0; HRMS (EI) calcd for C₁₈H₂₂O₃ (M⁺) *m/z* 286.1569, found 286.1569.

General Procedure for the Microwave-Assisted Cyclization/Claisen Rearrangement: Preparation of (3a*S**,4*R**)-4-(2,5-Dimethoxyphenyl)-2,3,3a,4,6,7-hexahydroazulen-5(1*H*)-one (**3**)

Alcohol **2** (100 mg, 0.35 mmol) was transferred to a 10 mL flame dried microwave vial along with anhydrous phenetole (1.5 mL) and a catalytic amount (ca. 10 mol-%) of MeLi in Et₂O, and the resulting mixture was heated at 210 °C for 45 min in the microwave oven. The phenetole solvent was then removed *in vacuo* and the residue was directly subjected to purification by column chromatography (5% to 10% EtOAc in hexane) to give ketone **3** as a pale yellow oil (76 mg, 76%). IR (neat) 2936, 1705, 1496, 1225, 823 cm⁻¹; ¹H NMR (CDCl₃, 500 MHz) δ 6.77-6.69 (m, 3 H), 5.56 (s, 1 H), 3.76 (s, 3 H), 3.72 (s, 3 H), 3.54-3.50 (m, 1 H), 3.48 (br s, 1 H), 2.49-2.45 (m, 3 H), 2.41-2.39 (m, 3 H), 1.65-1.59 (m, 1 H), 1.50-1.45 (m, 1 H), 1.42-1.36 (m, 1 H), 1.23-1.18 (m, 1 H); ¹³C NMR (CDCl₃, 125 MHz) δ 213.8, 153.4, 150.9, 146.1, 130.9,

118.9, 117.7, 112.0, 111.9, 61.3, 55.9, 55.6, 41.4, 40.7, 35.7, 34.0, 27.2, 24.6; HRMS (EI) calcd for $C_{18}H_{22}O_3$ (M^+) m/z 286.1569, found 286.1569.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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17. All stereochemical assignments were unambiguously determined by standard 1D NOSTY techniques and through examination of the relevant coupling constant between the benzylic proton and the adjacent bridgehead proton in each case.

SCHEME 1.

General strategy for the formation of substituted 4-cycloheptenones from secondary 4-pentyn-1-ols.

SCHEME 2.
Preparation of α -arylated hydroazulenone derivatives

SCHEME 3. Proposed mechanism for the formation of **15** and **15c**.

SCHEME 4.

Isomerization of a mixture of **17/17a** under basic conditions.

FIGURE 1.
Synthesis of fused seven-membered ring systems via the Claisen rearrangement.

TABLE 1

Synthesis of 4-cycloheptenone derivatives via tandem 5-exo dig cyclization/Claisen rearrangement sequence

Entry	4-Pentyn-1-ol	Product ^a	Yield (%) ^b
1	4	5	75
2	6	7	77
3	8	9	73
4	10	11	45
5	12	13	72
6	14	15 d.r.=92:8	77
7	2	3 d.r.=93:7	76
8	16	17 d.r.=77:23	82
9	18	19 d.r.=85:15	81
10	20	21	89

Entry	4-Pentyn-1-ol	Product ^a	Yield (%) ^b
11	22	d.r. = 67:33 23	60

^a All reactions were conducted in the microwave oven at 210 °C for 45 (entries 1,3,6-9) or 60 min in the presence of 10 mol-% MeLi and using phenetole as the solvent.

^b Isolated yields of chromatographically purified products.