JOC*Note*

Synthesis of Seven-Membered Carbocyclic Rings via a Microwave-Assisted Tandem Oxyanionic 5-*exo dig* Cyclization−Claisen Rearrangement Process

Xin Li, Robert E. Kyne, and Timo V. Ovaska*

Department of Chemistry, Connecticut College, 270 Mohegan Avenue, New London, Connecticut 06320

timo.ovaska@conncoll.edu

Received May 17, 2007

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] guianolides,[3] and 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 of 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 of polycyclic cycloheptanoid ring structures of the type shown in Figure 1 has not been widely utilized, most likely because of difficulties associated with the preparation of the requisite starting materials.

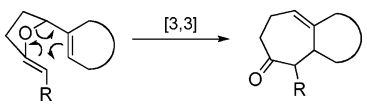
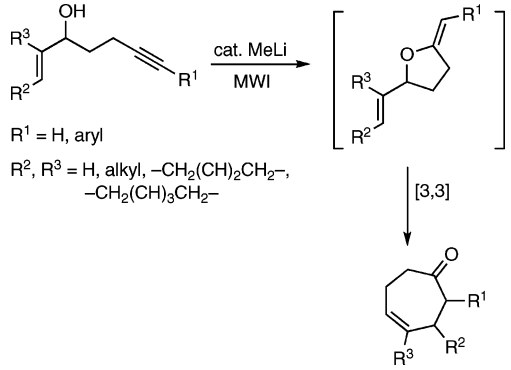
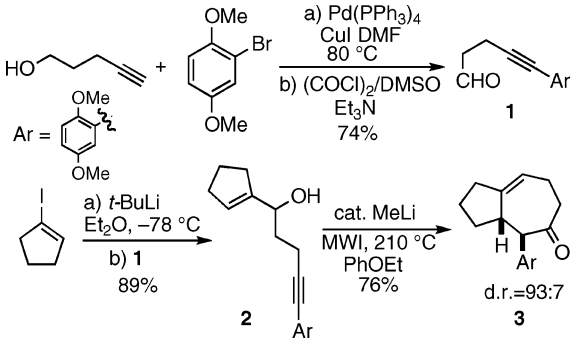


FIGURE 1. Synthesis of fused seven-membered ring systems via the Claisen rearrangement.

SCHEME 1. General Strategy for Formation of Substituted 4-Cycloheptenones from Secondary 4-Pentyn-1-ols



SCHEME 2. Preparation of α-Arylated Hydroazulenone Derivatives

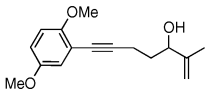
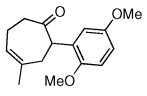
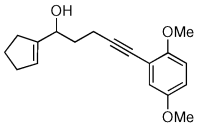
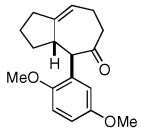
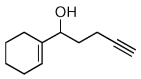
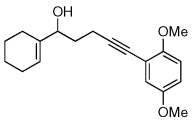
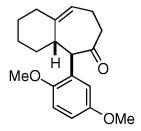
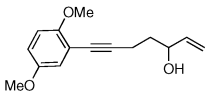
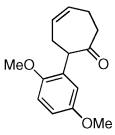
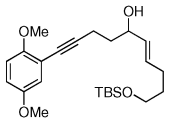
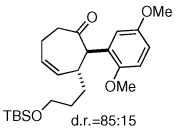
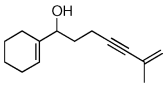
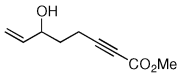
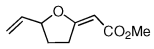
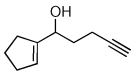
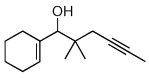
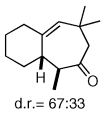
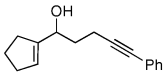


We have recently demonstrated that a variety of cycloheptanoid fused ring systems may be conveniently accessed through a known[7] but largely ignored tandem sequence that involves a base-catalyzed intramolecular cyclization of appropriately substituted tertiary acetylenic alcohols (4-pentyn-1-ols), followed 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-

(1) Evans, F. J., Ed. In *Naturally Occurring Phorbol Esters*; CRC: Boca Raton, FL, 1986.
(2) Bondi, S. M.; Clardy, J. *J. Am. Chem. Soc.* **2001**, *123*, 9900−9901.
(3) Wong, H.−F.; Brown, G. D. *J. Nat. Prod.* **2002**, *65*, 481−486.
(4) Patil, A. D.; Killmer, L.; Offen, P.; Carte, B.; Jurewicz, A. J.; Johnson, R. K. *Tetrahedron* **1997**, *53*, 5047−5060.
(5) For a recent review, see: Battiste, M. A.; Pelphrey, P. M.; Wright, D. L. *Chem. Eur. J.* **2006**, *12*, 3438−3447.
(6) Rhoads, S. J.; Brandenburg, C. F. *J. Am. Chem. Soc.* **1971**, *93*, 5805−5813.
(7) Marvell, E. N.; Titterington, D. *Tetrahedron Lett.* **1980**, 2123−2134.
(8) (a) Ovaska, T. V.; Roark, J. L.; Shoemaker, C. M. *Tetrahedron Lett.* **1998**, 39, 5705−5708. (b) Ovaska, T. V.; Roses, J. B. *Org. Lett.* **2000**, *2*, 2361−2364. (c) Ovaska, T. V.; Reisman, S. E.; Flynn, M. A. *Org. Lett.* **2001**, *3*, 115−117. (d) Ovaska, T. V.; Ravi Kumar, J. S.; Hulford, C. A.; O'Sullivan, M. F.; Reisman, S. E. *Tetrahedron Lett.* **2002**, *43*, 1939−1941.

10.1021/jo0710432 CCC: $37.00
Published on Web 07/27/2007

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]	Entry	4-Pentyn-1-ol	Product[a]	Yield (%)[b]
1	 **4**	 **5**	75	7	 **2**	 d.r.=93:7 **3**	76
2	 **6**	 **7**	77	8	 **16**	 d.r.=77:23 **17**	82
3	 **8**	 **9**	73	9	 **18**	 d.r.=85:15 **19**	81
4	 **10**	 **11**	45	10	 **20**	 **21**	89
5	 **12**	 **13**	72	11	 **22**	 d.r.= 67:33 **23**	60
6	 **14**	 d.r.=92:8 **15**	77				

[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.

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 to a variety of compounds containing substituted seven-membered rings, particularly mono- and bicyclic α,β-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 protocol[10] to give a known[11] 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 secondary alcohol **2** in 67% yield over three steps. On

(e) McIntosh, C. E.; Martinez, I.; Ovaska, T. V. *Synlett.* **2004**, 2579−2581. (f) Martinez, I.; Alford, P. E.; Ovaska, T. V. *Org. Lett.* **2005**, *7*, 1133−1135. (g) Li, X.; Kyne, R. E.; Ovaska, T. V. *Org. Lett.* **2006**, *8*, 5153−5156. (h) Li, X.; Kyne, R. E.; Ovaska, T. V. *Tetrahedron* **2007**, *63*, 1899−1906.

(9) For a recent review on transition-metal-catalyzed addition of heteroatom-hydrogen bonds to alkynes, see: Alonso, F.; Beletskaya, I. P.; Yus, M. *Chem. Rev.* **2004**, *104*, 3079−3159.

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]

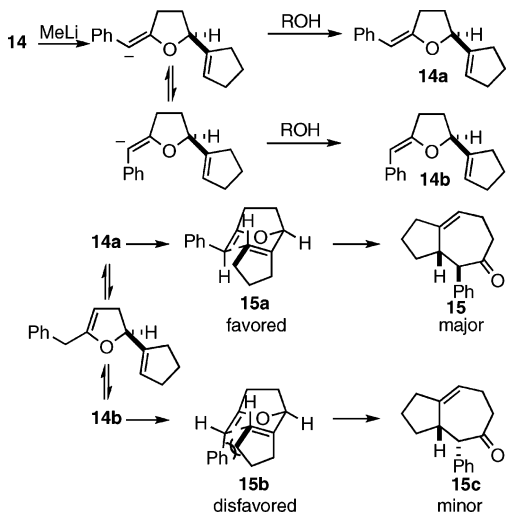
The tandem process also works well with alcohols bearing terminal triple bonds (Table 1, entries 2 and 5) and even alkyl-substituted secondary alcohols react provided that the initial ring closure is facilitated through operation of the Thorpe−Ingold effect.[14] Indeed, while simple alkyl-substituted 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 carbmethoxy derivative **20** also cyclized readily to afford the known tetrahydrofuranyl 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 the product (Table 1, entry 4). Results from these and other experiments are summarized in Table 1.

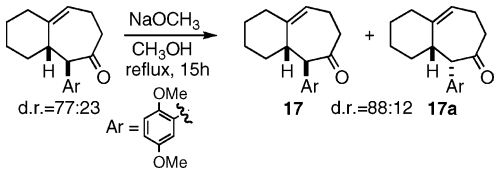
Reactions involving terminally substituted 4-pentyn-1-ols were found to be highly stereoselective, with R^1 and R^2 groups (Scheme 1) showing a strong preference for *trans* orientation in the final product. The observed stereochemical trends in these processes may be justified by invoking a chairlike 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 pseudoequatorial orientation (**15a**) is more favorable than that involving a pseudoaxial 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

SCHEME 3. Proposed Mechanism for Formation of 15 and 15c



SCHEME 4. Isomerization of a Mixture of 17/17a under Basic Conditions



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 15 h 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 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 of Et_2O was added *t*-BuLi (1.7 M

(10) Sonogashira, K.; Tohda, Y.; Hagihara, N. *Tetrahedron Lett.* **1975**, 4467−4470.

(11) Brimble, M. A.; Pavia, G. S.; Stevenson, R. J. *Tetrahedron Lett.* **2002**, *43*, 1735−1738.

(12) Mancuso, A. J.; Swern, D. *Synthesis* **1981**, 165−185.

(13) (a) Palucki, M.; Buchwald, S. L. *J. Am. Chem. Soc.* **1997**, *119*, 11108−11109. (b) Fox J. M.; Huang, X.; Chieffi, A.; Buchwald, S. L. *J. Am. Chem. Soc.* **2000**, *122*, 1360−1370. (c) Hamann, B. C.; Hartwig, J. F. *J. Am. Chem. Soc.* **1997**, *119*, 12382−12383.

(14) Beesley, R. M.; Ingold, C. K.; Thorpe, J. F. *J. Chem. Soc.* **1915**, *107*, 1080−1106.

(15) [3,3]-Sigmatropic rearrangement of **21** to afford 2-carbmethoxy-4-cycloheptenone on prolonged heating has been previously observed; see: Tsuji, J.; Kobayashi, Y.; Takahashi, T. *Tetrahedron Lett.* **1980**, *21*, 1475−1476.

(16) Hunter, D. H.; Cram, D. J. *J. Am. Chem. Soc.* **1964**, *86*, 5478−5490.

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

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 recooling to −78 °C, aldehyde **1** (436 mg, 2.00 mmol) in Et_2O (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 NH_4Cl. The layers were separated, and the aqueous layer was extracted with Et_2O. The combined organic extracts were washed with brine, dried over $MgSO_4$, 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 ($CDCl_3$, 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); ^{13}C NMR ($CDCl_3$, 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 $C_{18}H_{22}O_3$ (M^+) *m*/*z* 286.1569, found 286.1569.

General Procedure for 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 Et_2O, 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 ($CDCl_3$, 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); ^{13}C NMR ($CDCl_3$, 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.

Acknowledgment. This research was supported by a grant from the National Institutes of Health (NIGMS). T.V.O also gratefully acknowledges support from the Hans and Ella McCollum-Vahlteich '21 endowment. R.E.K. gratefully acknowledges support from Bristol-Myers Squibb and the Connecticut Business and Industry Association.

Supporting Information Available: Experimental procedures, characterization data, and copies of ^1H and ^{13}C NMR spectra for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

JO0710432