ORGANIC LETTERS

2000
Vol. 2, No. 15
2361−2364

Tandem Anionic 5-Exo Dig Cyclization/ Claisen Rearrangement as an Efficient Route to Fused Polycyclic Ring Systems

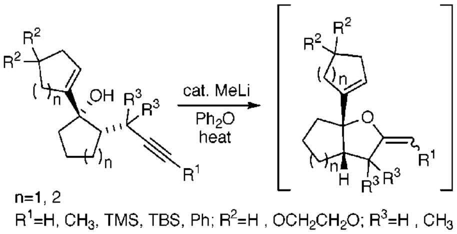
Timo V. Ovaska* and Jonathan B. Roses

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

tvova@conncoll.edu

Received May 31, 2000

ABSTRACT

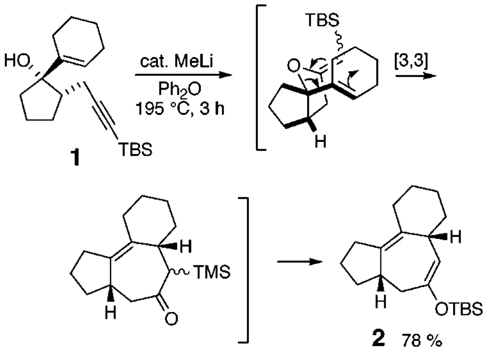


The scope and limitations of a tandem 5-exo dig cyclization/Claisen rearrangement sequence involving appropriately substituted 4-alkyn-1-ols as an efficient "one-pot" route to fused tricyclic ring systems is described. The reaction rates were found to be strongly dependent on the nature of the terminal substitutent of the triple bond. In some cases the entire sequence was found to proceed in good yield at temperatures as low as 115 °C.

We have recently reported[1] that a tandem anionic 5-exo dig cyclization/Claisen rearrangement sequence, first described by Marvell and Titterington in 1980,[2] can be used to generate rather complex polycyclic structures in a short sequence of steps from simple starting materials. As depicted in Scheme 1, the tricyclic product **2** was obtained as a single diastereomer in 78% isolated yield simply by treatment of **1** with a catalytic (10−15 mol %) amount of MeLi in diphenyl ether at 195 °C. It is noteworthy that in cases where the triple bond bears a silicon-containing substituent (TMS or TBDMS) the Claisen rearrangement is accompanied by the Brook rearrangement,[3] providing a silyl enol ether as the ultimate reaction product.[1]

In our initial studies involving a limited number of substrates, relatively high-temperature conditions (195 °C) were employed, and although no product decomposition was observed in the cases studied, it was obvious that less forcing

Scheme 1

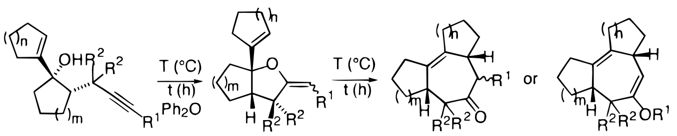


---

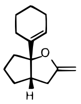
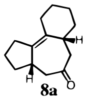
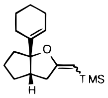
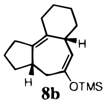
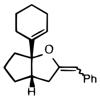
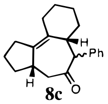
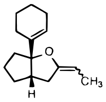
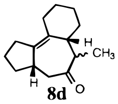
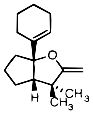
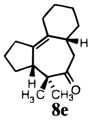
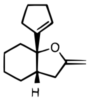
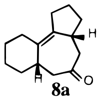
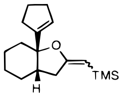
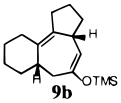
[1] Ovaska, T. V.; Roark, J. L.; Shoemaker, C. M. *Tetrahedron Lett.* **1998**, *39*, 5705.
[2] Marvell, E. N.; Titterington, D. *Tetrahedron Lett.* **1980**, 2123.
[3] Brook, A. G. *Acc. Chem. Res.* **1974**, *7*, 77.

10.1021/ol006139w CCC: $19.00

Table 1. 5-Exo Dig Cyclization/Claisen Rearrangement of Compounds **4a**–**e** and **5a**–**b**



4 n=2, m=1 **6** n=2, m=1 **8** n=2, m=1
5 n=1, m=2 **7** n=1, m=2 **9** n=1, m=2

4-alkyn-1-ol	R^1	R^2	T, °C	t^a, h	cyclic intermediate	t^b, h	product	isolated yield (%)
4a	H	H	115 135 160	1.0 <0.5 <0.5		49^c 20^d 1.0	 **8a**	76
4b	TMS	H	145 165	2.0 <1.0		23 10.5	 **8b**	85^e
4c	Ph	H	190 140 115	<0.5 1.5 2.5		<0.5 2.0 3.0	 **8c**	55^f
4d	Me	H	195	$–^g$		2.0	 **8d**	76^h
4e	H	Me	170 80 18^i	<0.5 <0.5 2.0		6.0 – –	 **8e**	81
5a	H	H	185 160	<0.5 <0.5		<1.0 10	 **8a**	83
5b	TMS	H	185	<0.5		2.0	 **9b**	70^e

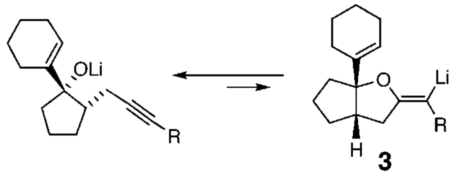
[a] Time required for the starting material to disappear. [b] Time required for the entire tandem sequence to proceed to completion. [c] Reaction was stopped at 81% conversion (determined by GC). [d] Reaction was stopped at 77% conversion (determined by GC). [e] Isolated yield reflects that of the hydrolysis product (aqueous 10% HCl), **8a**. [f] Product was obtained as a 3:2 mixture of diastereomers. [g] Cyclic intermediate not detected in this case. [h] Product was obtained as a 7:1 mixture of diastereomers. [i] THF was used as the solvent.

conditions would greatly enhance the synthetic utility of this tandem sequence. In this communication, we wish to report the results of our systematic study probing the scope and limitations of this metholodology.

The α-propargyl-substituted cyclic ketones required for this study were prepared in a straightforward fashion using standard enolate chemistry or by employing nucleophilic epoxide ring opening of cycloalkene oxides, followed by oxidation of the resulting alcohols. The requisite 4-alkyn-1-ol systems (compounds **4a**–**e** and **5a**–**b**, Table 1) were synthesized as described before[1] by reacting the appropriate acetylenic ketones with cycloalkenylcerium dichlorides, which in turn were generated in situ from the corresponding vinyllithium species.

Each of the 4-alkyn-1-ol systems were subjected to catalytic MeLi (~10 mol %) at different temperatures, and the progress of the reactions was monitored using a gas chromatograph equipped with a flame-ionization detector. In the majority of cases examined, disappearance of the starting material was first accompanied by buildup of the cyclic tetrahydrofuran intermediate, which then gradually rearranged to the final tricyclic product. The results of these experiments are summarized in Table 1.

On the basis of literature precedent involving anionic cyclizations of acetylenic alkyl- and vinyllithiums,[4] we anticipated that groups capable of stabilizing the incipient vinylanion species (**3**, R = Ph or TMS) would also facilitate the initial cycloisomerization of the alkoxide anion. Thus, it was expected that substrates bearing silyl or aryl substituents on the triple bond terminus would cyclize faster than the corresponding alkyl-substituted systems. Indeed this turned out to be the general trend.



We found that both the trimethylsilyl- and the phenyl-substituted derivatives, **4b** and **4c**, reacted at temperatures considerably lower than those reported earlier.[1] Thus, the phenyl derivative **4c** cyclized in about 2 h at 115 °C to give **6c**, which then underwent subsequent [3,3] sigmatropic rearrangement at the same temperature to afford the tricycle **8c** as a 3:2 mixture of epimers.[5] The total reaction time in this case (**4c** to **8c**) was less than 3 h.

As expected, the corresponding methyl derivative proved more resistant to cycloisomerization. In fact, no accumulation of the intermediate **6d** was detected under the high-temperature conditions employed, suggesting that once formed, it rearranges rapidly to provide the final Claisen product. Thus, it appears that in cases where the triple bond is alkyl-substituted, the relative rates of 5-exo isomerization vs Claisen rearrangement follow opposite trends compared to the analogous silyl- or aryl-substituted derivatives, with the initial cyclization being rate-determining.

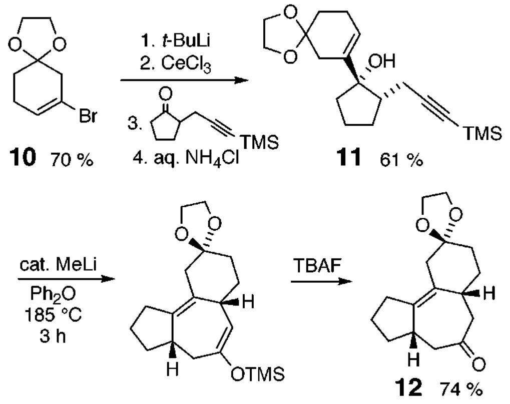
Somewhat surprisingly, we found that cyclization of the unsubstituted derivative **4a** proceeded faster than either the silyl- or phenyl-substituted analogues. Thus, cycloisomerization of **4a** was effected in less than an hour at temperatures as low as 115 °C. Under these conditions, a steady increase of the Claisen product was also observed, and after 49 h, 81% of the product mixture consisted of the final tricyclic ketone, the balance of the reaction (19%) being the intermediate cyclized product.

Rate enhancement of the initial cycloisomerization was even greater for the *gem*-dimethyl derivative **4e**, which can be expected to further benefit from operation of the Thorpe–Ingold effect.[6] In this case, the initial cyclization proceeded rapidly even at ambient temperature; however, the subsequent sigmatropic rearrangement occurred more slowly, requiring 6 h at 170 °C to proceed to completion. This is most likely due to unfavorable steric interactions engendered by the *gem*-dimethyl moiety in the transition state of the Claisen rearrangement.

As shown in Table 1, this tandem reaction sequence also works well in cases where acetylenic cyclohexanols instead of cyclopentanol derivatives are used (**5a** and **5b**) as starting materials. Thus, **5a** undergoes MeLi-catalyzed cyclization to provide the intermediate 2-methyleneoctahydrobenzofuran derivative **7a**, and the subsequent Claisen rearrangement is effected on continued heating to yield **8a**, identical in all respects with that obtained from **4a** (or **4b** following acid hydrolysis). These results suggest that, by simply varying the size of the cycloalkanol and cycloalkenyl ring fragments in the starting 4-alkyn-1-ols, the methodology at hand should be applicable to the construction of a variety of cycloheptenone-containing polycyclic ring systems.

As shown in Scheme 2, the introduction of an acetal functionality into the TMS-substituted acetylenic alcohol **11** was accomplished in a straightforward manner by coupling vinyl bromide **10**[7] with 2-(3-trimethylsilyl-2-propynyl)-cyclopentanone.[1] Upon exposure to catalytic amounts of MeLi and heat followed by treatment of the resulting silyl enol ether with TBAF, **11** was subsequently converted to the tricyclic monoacetal-protected diketone **12** in 74% isolated yield. Significantly, no decomposition of the acetal moiety was noted under these conditions.

Scheme 2



Alternatively, the acetal-protected tetracycle **15** (regioisomer of **12**) can be constructed from alkynol **14**, which in turn is accessible in two steps from commercially available 1,4-cyclohexanedione monoethylene ketal as shown in Scheme 3.

In conclusion, we have shown that sequential 5-exo dig cyclization/Claisen rearrangement process involving ap-

---

(4) (a) Bailey, W. F.; Ovaska, T. V. *J. Am. Chem. Soc.* **1993**, *115*, 3080. (b) Ovaska, T. V.; Warren, R. R.; Lewis, C. E.; Wachter-Jurcsak, N.; Bailey, W. F. *J. Org. Chem.* **1994**, *59*, 5868. (c) Bailey, W. F.; Wachter-Jurcsak, N. M.; Pineau, M. R.; Ovaska, T. V.; Lewis, C. E.; Warren, R. R. *J. Org. Chem.* **1996**, *61*, 8216.

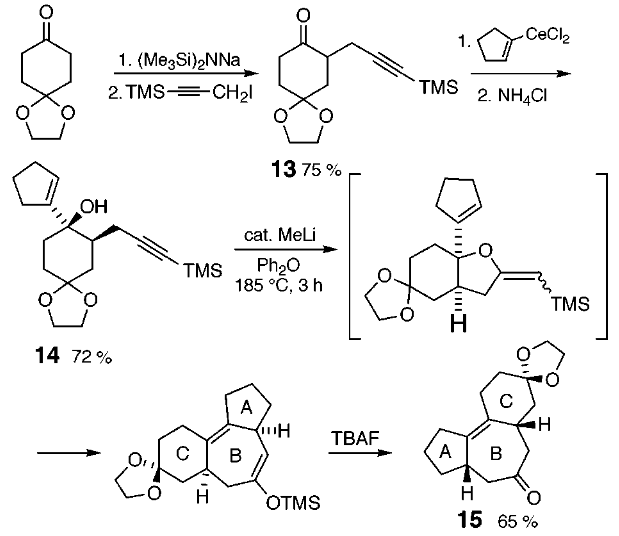
(5) The formation of diastereomers in this case undoubtedly results from *cis-trans*-isomerization of the incipient α-phenyl-substituted vinylanion species **3** prior to the rearrangement. See, e.g., Hunter, D. H.; Cram, D. J. *J. Am. Chem. Soc.* **1964**, *86*, 5478.

(6) Allinger, N. L.; Zalkov, V. *J. Org. Chem.* **1960**, *25*, 701.

(7) Bromide **10** was prepared in two steps from 1,3-cyclohexanedione according to the procedure of Swenton et al.: Swenton, J. S.; Shih, C. *J. Org. Chem.* **1982**, *47*, 2825.

(8) Ovaska, T. V.; Flynn, M. A.; Roses, J.; Berns, D. *Abstracts of Papers*, 219th National Meeting of the American Chemical Society, San Francisco, CA, 2000; American Chemical Society: Washington, DC, 2000; ORGN 840.

Scheme 3



propriately substituted 4-alkyn-1-ols provides an efficient one-pot route to fused tricyclic ring systems. The reaction appears to be general and works well regardless of the nature of the substitutent on the triple bond terminus. However, marked differences in reaction rates were observed between the various substrates examined, the methyl-substituted system **4d** requiring more forcing conditions than either the unsubstituted derivative **4b** or those bearing phenyl or trimethylsilyl groups on the triple bond. We are currently in the process of applying this methodology to the synthesis of more functionalized and elaborate ring systems, including those containing the tetracyclic 5-7-6-3 phorbol nucleus.[8]

Acknowledgment. This work was supported by grants from the donors Petroleum Research Fund, administered by the American Chemical Society, the Research Corporation (Cottrell College Science Award), and the National Institutes of Health (GM60972-01). J.B.R. acknowledges Pfizer, Inc. for a Summer Fellowship (PREPARE program).

Supporting Information Available: Detailed experimental procedures with spectroscopic data for compounds **4a**, **4d**, **5a**−**b**, **8d**−**e**, and **11**−**15**. This material is available free of charge via the Internet at http://pubs.acs.org.

OL006139W