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Anionic Two-Carbon Ring Expansions of Oxabicyclo[2.2.1]heptenes and Oxabicyclo[4.2.1]nonenes

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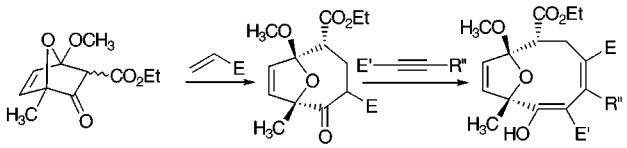
ABSTRACT



This Letter describes the synthesis of oxabicyclo[4.2.1]nonenes and oxygen-bridged cyclodecenes from the anionic two-carbon ring expansions of oxabicyclo[2.2.1]heptenes and oxabicyclo[4.2.1]nonenes, respectively.

As part of our program targeting the synthesis of furan-containing natural products, we recently communicated a novel tandem sequence which resulted in the synthesis of substituted furans and cyclopentenes from the anionic condensation of bicyclo[2.2.1]heptene β-keto esters with aldehydes.[1] Although unsubstantiated, we had rationalized our results by invoking the fragmentation of fused oxetane intermediates.

Assuming that the aldehyde condensation mechanism was applicable, we believed that the anionic coupling of bicyclo-[2.2.1]heptene β-keto esters with activated alkenes would result in the formation of bicyclo[4.2.1]nonenes.[2,3] Not only would these ring-expanded products be synthetically useful in their own right[4] but they might also be susceptible to a subsequent two-carbon ring expansion.[5] We were intrigued by this possibility, as the result of the second ring expansion would be an oxygen-bridged cyclodecene ring system as is present in both the heliangolides[6,7] as well as the oxygenated cembranoids.[8,9] Contained herein is the successful implementation of this strategy.

With the proposed mechanism for the aldehyde condensation and fragmentation in mind, we set out to investigate the anionic coupling of **1**[1] with Michael acceptors. The addition of methyl acrylate to a solution of β-keto ester **1**, NaH, and DMF resulted in the isolation of oxabicyclo[4.2.1]-nonenes **2** and **3** as a readily separable 3.3:1 mixture of C-4 isomers (Table 1, entry 1).[10] It is interesting to note that while

(1) Rainier, J. D.; Xu, Q. *Org. Lett.* **1999**, *1*, 27−29.

(2) For a recent example of a β-keto ester−Michael addition reaction which leads to bicyclic ring systems see: Aoyagi, K.; Nakamura, H.; Yamamoto, Y. *J. Org. Chem.* **1999**, *64*, 4148−4151.

(3) For related ring expansions see: (a) Xie, Z.-F.; Sakai, K. *J. Org. Chem.* **1990**, *55*, 820−826. (b) Lavoisier-Gallo, T.; Charonnet, E.; Rodriguez, J. *J. Org. Chem.* **1998**, *63*, 900−902.

(4) We envision that **2** and **3** (Table 1) will be useful in the formation of medium-sized rings. For example, oxidative carbon−carbon bond fragmentation would lead to the corresponding oxepanes. Ketal hydrolysis would result in the synthesis of the corresponding cyclooctenones.

(5) (a) Chenna, A.; Donnelly, J.; McCullough, K. J.; Proctor, G. R.; Redpath, J. *J. Chem. Soc., Perkin Trans. 1* **1990**, 261−265. (b) Frew, A. J.; Proctor, G. R. *J. Chem. Soc., Perkin Trans. I* **1980** 1245−1250. (c) Frew, A. J.; Proctor, G. R. *J. Chem. Soc., Perkin Trans. I* **1980**, 1251−1256.

(6) For representative examples of this family see: (a) Barrero, A. F.; Oltra, J. E.; Raslan, D. S.; Saude, D. A. *J. Nat. Prod.* **1999**, *62*, 726−729. (b) Baruah, N. C.; Sharma, R. P.; Madhusudanan, K. P.; Thyagarajan, G.; Herz, W. Murari, R. *J. Org. Chem.* **1979**, *44*, 1831−1835. (c) Raffauf, R. F.; Huang, P.-K. C.; Le Quesne, P. W.; Levery, S. B.; Brennan, T. F. *J. Am. Chem. Soc.* **1975**, *97*, 6884−6886.

(7) For the total synthesis of heliangolides see: (a) Boeckman, R. K., Jr.; Yoon, S. K.; Heckendorn, D. K. *J. Am. Chem. Soc.* **1991**, *113*, 9682−9684. (b) Takao, K.; Ochiai, H.; Yoshida, K.; Hashizuka, T.; Koshimura, H.; Tadano, K.; Ogawa, S. *J. Org. Chem.* **1995**, *60*, 8179−8193.

(8) Bernardelli, P.; Paquette, L. A. *Heterocycles* **1998**, *49*, 531−556.

(9) For the total synthesis of oxygenated cembranoids see: (a) MacMillan, D. W. C.; Overman, L. E. *J. Am. Chem. Soc.* **1995**, *117*, 10391−10392. (b) Nicolaou, K. C.; Xu, J. Y.; Kim, S.; Pfefferkorn, J.; Ohshima, T.; Vourloumis, D.; Hosokawa, S. *J. Am. Chem. Soc.* **1998**, *120*, 8661−8673. (c) Nicolaou, K. C.; Ohshima, T.; Hosokawa, S.; van Delft, F. L.; Vourloumis, D.; Xu, J. Y.; Pfefferkorn, J.; Kim, S. *J. Am. Chem. Soc.* **1998**, *120*, 8674−8680. (d) Chen, X.-T.; Zhou, B.; Bhattacharya, S. K.; Gutteridge, C. E.; Pettus, T. R. R.; Danishefsky, S. J. *Angew. Chem., Int. Ed.* **1998**, *37*, 185−187.

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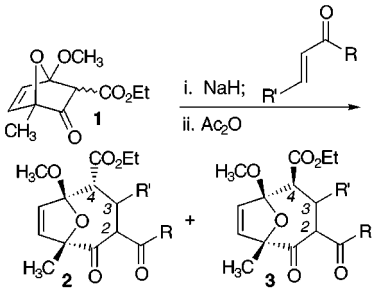
Table 1. Two-Carbon Ring Expansions of Oxabicyclo[2.2.1]heptenones



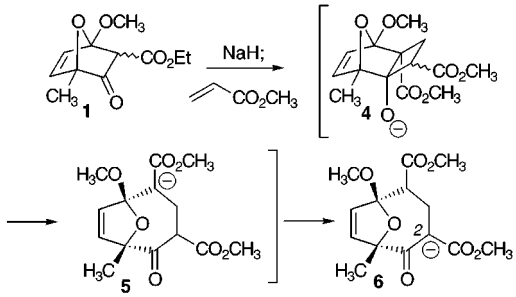
Entry	R	R'	Yield	2:3[a]
1	OCH_3	H	70%	3.3:1
2	OCH_3	CO_2CH_3	70%	3.3:1[b]
3	$O(CH_2)_2CHCH_2$	H	79%	3.4:1
4	CH_3	H	53%	3:1

[a] obtained from the ^{1}H NMR spectrum of the crude material
[b] **3** was obtained as a 1:1 mixture of C-3 diastereomers

3 was isolated as a single compound, **2** was isolated as a 1:1 mixture of C-2 diastereomers. As was the case in our previously disclosed aldehyde investigations, we had condensed, cyclized, and fragmented in a single flask. This sequence appears to be general, as dimethyl fumarate, 3-butenyl acrylate, and methyl vinyl ketone also gave ring-expanded products (Table 1, entries 2−4, respectively).

We believe that our results are consistent with an ionic bond-forming and -breaking sequence. As outlined in Scheme 1, it appears likely that conjugate addition is followed by

Scheme 1



cyclization to give the corresponding cyclobutane intermediate **4**.[11] Fragmentation of **4** leads to the observed products. If this hypothesis is correct, the reaction is undoubtedly driven by relief of ring strain as well as formation of β-keto ester anion **6**.[12]

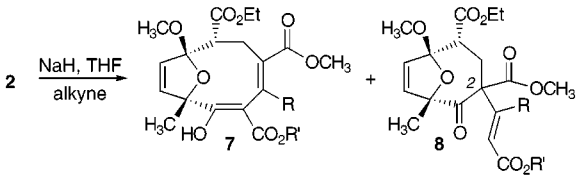
(10) The relative stereochemistry at C-4 in **2** and **3** was determined by first converting each of them into the corresponding enol acetate and then identifying the expected NOESY cross-peaks.

(11) Proctor has proposed a similar mechanism in the two-carbon ring expansion of β-keto esters.[5b]

(12) We were able to incorporate deuterium at C-2 by quenching the reaction with D_2O.

With an efficient route to oxabicyclo[4.2.1]nonene β-keto esters **2** and **3** in hand, we targeted their anionic two-carbon ring expansion reactions with activated alkynes. We were reasonably confident that these transformations would be successful, as anionic two-carbon ring expansions of β-keto esters are precedented, albeit in less functionalized systems.[5] As depicted in Table 2, these reactions lead to oxygen-

Table 2. Anionic Two-Carbon Ring Expansions of **2**



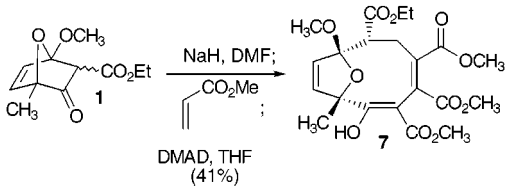
Entry	Alkyne	R	R'	Yield	7:8
1	$MeO_2C{-}{\equiv}{-}CO_2Me$	CO_2Me	Me	92%	1:0
2	$EtO_2C{-}{\equiv}{-}H$	H	Et	44%	1:1.3[a]

[a] **8** was isolated as a 1:1 mixture of C-2 diastereomers

bridged cyclodecene ring systems. Interestingly, while both DMAD and ethyl propiolate undergo a reasonably efficient Michael addition reaction with **2** (R = OCH_3, R′ = H), the resulting DMAD adduct was much more effective at the subsequent ring expansion reaction.[13] That is, while the use of DMAD resulted in the formation of **7** (R = CO_2CH_3, R′ = CH_3) in 92% yield, the use of ethyl propiolate resulted in the formation of a 1:1.3 mixture of ring-expanded and Michael adducts in 44% yield. We are particularly pleased with the efficiency with which **7** (R = CO_2CH_3, R′ = CH_3) has been synthesized, as this ring system is a key structural unit in both the oxygenated cembranoid marine natural products[8] as well as the sesquiterpene lactone containing heliangolides.[6]

Having successfully demonstrated a two-flask, four-carbon ring expansion, we set out to carry out this transformation in a single flask. We believed that conditions for this reaction could be identified because of the proton transfer that was

Scheme 2



alluded to earlier.[12] In practice, when the β-keto ester anion from **1** was subjected to methyl acrylate followed by DMAD, **7** (R = CO_2CH_3, R′ = CH_3) was isolated in an unoptimized 41% yield (Scheme 2).

(13) β-Keto ester **3** (R = OCH_3, R′ = H) is much less efficient in the two-carbon ring expansion reaction (21% yield using DMAD).

To conclude, this letter has described anionic two-carbon ring expansions of oxabicyclo[2.2.1]heptenes and oxabicyclo-[4.2.1]nonenes. These reactions result in the efficient formation of oxabicyclo[4.2.1]nonenes and oxygen-bridged cyclodecene skeletons, respectively. The efficiency of these ring expansion reactions bodes favorably for their use in the synthesis of bioactive targets which contain medium-sized rings.

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Supporting Information Available: Experimental procedures and spectroscopic data for compounds **2**, **3**, **7**, and **8**. This material is free of charge via the Internet at http://pubs.acs.org.

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