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A Novel Anionic Condensation, Fragmentation, and Elimination Reaction of Bicyclo[2.2.1]heptenone Ring Systems

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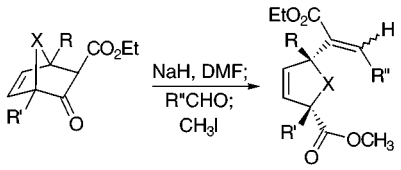
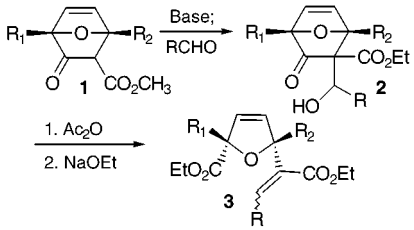
ABSTRACT



We have identified an unprecedented anionic condensation, fragmentation, and elimination sequence from the coupling of bicyclo[2.2.1]-heptenones with aldehydes. This reaction leads to the stereoselective formation of disubstituted five-membered rings which are present in a wide array of bioactive molecules.

Substituted furans are a key architectural feature in a wide array of biologically active molecules. Our interest in the 2,5-disubstituted furan-containing marine natural products gymnodimine[1,2] and eleutherobin[3,4] has directed our attention to the synthesis of these structural units. As envisioned, our approach to the synthesis of substituted furans included (a) an aldol condensation between an oxabicyclo[2.2.1]heptenone[5] and an aldehyde, (b) a subsequent fragmentation reaction,[6] and (c) an elimination reaction to the corresponding olefin (Scheme 1). As described in this Letter, in the course of these investigations we have uncovered an unprecedented anion-mediated condensation, fragmentation, and elimination reaction during which all of the goals outlined above were accomplished in a single flask.[7]

Scheme 1. Sequential Diels−Alder, Condensation, and Fragmentation Approach to 2,5-Disubstituted Furans



To investigate the sequence depicted in Scheme 1, we initially examined the condensation of oxabicyclo[2.2.1]-

(1) (a) Seki, T.; Satake, M.; Mackenzie, L.; Kaspar, H. F.; Yasumoto, T. *Tetrahedron Lett.* **1995**, *36*, 7093−7096. (b) Stewart, M.; Blunt, J. W.; Munro, M. H. G.; Robinson, W. T.; Hannah, D. J. *Tetrahedron Lett.* **1997**, *38*, 4889−4890.

(2) For synthetic efforts to gymnodimine, see: Ishihara, J.; Miyakawa, J.; Tsujimoto, T.; Murai, A. *Synlett.* **1997**, 1417−1419.

(3) Lindel, T.; Jensen, P. R.; Fenical, W.; Long, B. H.; Casazza, A. M.; Carboni, J.; Fairchild, C. R. *J. Am. Chem. Soc.* **1997**, *119*, 8744−8745.

(4) Two total syntheses of eleutherobin have appeared. See: (a) Nicolaou, K. C.; van Delft, F.; Ohshima, T.; Vourloumis, D.; Xu, J. H., S.; Pfefferkorn, J.; Kim, S.; Li, T. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 2520−2524. (b) Chen, X.-T.; Zhou, B.; Bhattacharya, S. K.; Gutteridge, C. E.; Pettus, T. R. R.; Danishefsky, S. J. *Angew. Chem., Int. Ed. Engl.* **1998**, *37*, 789−792.

(5) Available from a furan Diels−Alder reaction. For a relevant review, see: Kappe, C. O.; Murphree, S. S.; Padwa, A. *Tetrahedron* **1997**, *53*, 14179−14233.

(6) For other uses of oxabicyclo[2.2.1] fragmentation reactions in the synthesis of substituted furans, see ref 5.

(7) Acid-mediated Aldol−Grob fragmentations have been described. See: (a) Kabalka, G. W.; Tejedor, D.; Li, N.-S.; Malladi, R. R.; Trotman, S. *J. Org. Chem.* **1998**, *63*, 6438−6439. (b) Yamamoto, T.; Suemune, H.; Sakai, K. *Tetrahedron* **1991**, *47*, 8523−8528.

(8) The trisubstituted olefin geometry was determined through the identification of the appropriate NOESY cross-peaks (see the Supporting Information for more details).

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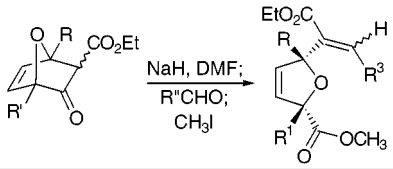
heptenone **4** with benzaldehyde (Table 1, entry 1). Surprisingly, rather than the simple condensation product, we isolated disubstituted furan **5** exclusively as its *Z*-alkene isomer in 83% yield after esterification. To our delight, we had achieved the condensation, fragmentation, and elimination in a single flask.

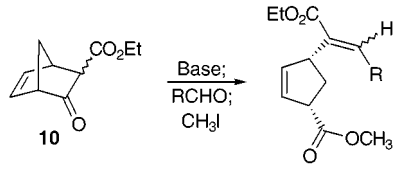
Table 1. Single Flask Condensation, Fragmentation, and Elimination to 2,5-Disubstituted Dihydrofurans



Entry	Ketone	R	R^1	R^3	Furan	Yield	*E:Z*
1	**4**	OCH_3	CH_3	Ph	**5**	83%	0:1
2	**4**	OCH_3	CH_3	*i*-Pr	**6**	78%	0:1
3	**7**	H	H	Ph	**8**	56%	3:1
4	**7**	H	H	*i*-Pr	**9**	45%	1:2

With the notion that this reaction might lead to the efficient synthesis of a number of substituted furans, we set out to determine the scope. As is depicted in Tables 1 and 2, other aldehydes and bicyclo[2.2.1] ring systems successfully underwent the reaction. For example, the condensation of isobutyraldehyde with **4** gave furan **6** exclusively as the *Z*-alkene isomer in 78% yield (Table 1, entry 2). The reaction is not specific to **4** as unsubstituted oxabicyclo[2.2.1]-*β*-keto ester **7** also underwent the condensation, fragmentation, and elimination reaction sequence. The unoptimized coupling of **7** with benzaldehyde and isobutyraldehyde gave furans **8** and **9**, respectively (Table 1, entries 3 and 4). Interestingly, while **4** gave exclusively the *Z*-alkene isomer with both benzaldehyde and isobutyraldehyde, **7** gave a 3:1 *E:Z* alkene mixture when condensed with benzaldehyde and a 1:2 *E:Z* mixture when condensed with isobutyraldehyde.[8]

Table 2. Single Flask Condensation, Fragmentation, and Elimination to 1,4-Disubstituted Cyclopentenes

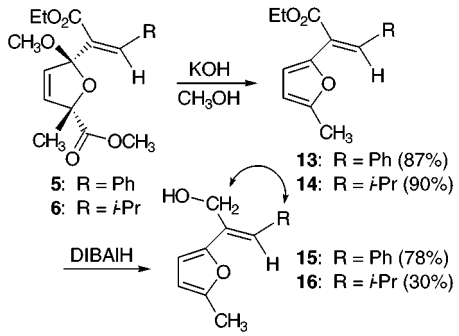


entry	R	Base	Cyclopentene	Yield	*E:Z*
1	Ph	KO*t*-Bu	**11**	91%	1:0
2	*i*-Pr	KO*t*-Bu	**12**	91%	3:1
3	*i*-Pr	NaH	**12**	94%	3:1

We have also examined the reaction between bicyclo[2.2.1]heptenone **10** and aldehydes (Table 2). As with the synthesis of the furans mentioned previously, the condensation, fragmentation, and elimination reaction of **10** with benzaldehyde and isobutyraldehyde proceeded smoothly to give cyclopentenes **11** and **12**, respectively. However, in contrast to **4** and **7**, the condensation of **10** with benzaldehyde and isobutyraldehyde gave predominantly or exclusively the *E*-alkene isomer.[8]

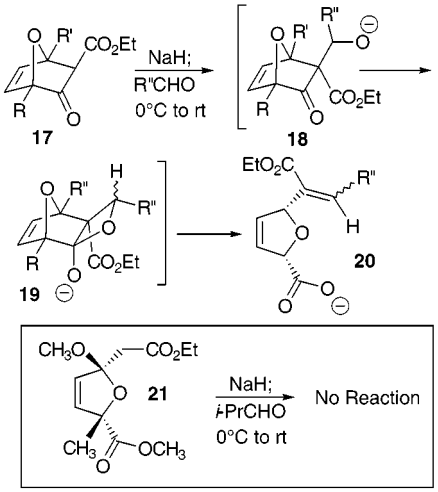
In contrast to **8**, **9**, **11**, and **12**, the NOESY spectra of substituted furans **5** and **6** were devoid of information. However, we were able to determine the olefin geometry in **5** and **6** after derivatization of the furan (Scheme 2). That is, treatment of **5** and **6** with methanolic KOH resulted in hydrolysis, decarboxylation, and aromatization to give **13** and **14**, respectively. DIBAL reduction gave allyl alcohols **15** and **16**.[9] As depicted, NOESY cross-peaks were observed between the isopropyl/phenyl hydrogens and the methylene hydrogens of the hydroxy methyl group, thereby establishing the trisubstituted olefin geometry.

Scheme 2. Determination of the Olefin Geometry in Furans **5** and **6**



While any detailed mechanistic discussion requires further experimentation, a reasonable working hypothesis is depicted in Scheme 3. It is highly likely that aldol condensation to

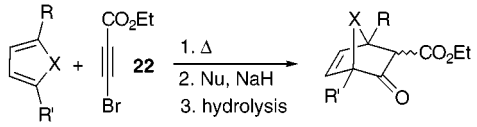
Scheme 3. Possible Mechanism for the Condensation, Fragmentation, and Elimination Reaction of Bicyclo[2.2.1]heptenes



give **18** precedes fragmentation as attempted aldol coupling between furan **21**[10] and isobutyraldehyde resulted in the recovery of **21**. Lactol formation provides oxetane **19**.[7] Oxetane fragmentation then leads to furan **20**. The nature of the substrate dependence on the *E*,*Z*-olefin selectivity is not readily apparent and is thus the focus of our current efforts.[11]

The bicyclo[2.2.1] ring systems used in this study are readily accessible using a Diels−Alder cycloaddition reaction between bromopropynoate **22** and the appropriate diene (Scheme 4).[12−14] A subsequent two-step hydrolysis of the resulting bromoacrylate derivative gave β-keto esters **4**, **7**, and **10**.

Scheme 4. Diels-Alder Approach to Bicyclo[2.2.1]heptenes



To conclude, we have identified a novel anion-mediated condensation, fragmentation, and elimination reaction of bicyclo[2.2.1]heptene ring systems. Our current efforts are focusing on the nature of the selectivity in this reaction as well as its use in the synthesis of furan-containing natural products.

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Supporting Information Available: Experimental procedures and spectroscopic data for compounds **4**−**12**, **15**, and **16**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(9) Thus far, we have been unable to selectively reduce the ethyl ester in **5** or **6**.
(10) **21** is available from the reaction of **4** and $NaOCH_3$.
(11) Thus far, our attempts to equilibrate the olefin in **5** with base have been unsuccessful.
(12) Sherman, E.; Dunlop, A. P. *J. Org. Chem.* **1960**, *25*, 1309−1311.
(13) Chamberlin, P.; Rooney, A. E. *Tetrahdedron Lett.* **1979**, 383−386.
(14) Leroy, J. *Tetrahdedon Lett.* **1992**, *33*, 2969−2972.