The MARDi Cascade: A New Base-Induced Five-Step Anionic Domino Reaction for the Stereoselective Preparation of Functionalized Cycloheptenes

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Among the growing number of useful sequential transformations used in organic chemistry, domino reactions,[1] which are also widely involved in nature, emerge as a powerful synthetic tool providing both an economical and ecological access to complex molecules. Cascades of more than three different reactions are still rare, and metal-catalyzed sequences largely lead the way over ionic processes.[2] In this context, we have been recently interested in developing anionic methodologies based on the reactivity of stabilized carbanions for stereoselective synthesis of bicyclo[3.2.1]octanols,[3] arylidenecycloalkanones,[4] cycloheptanols,[5] and cyclooctane derivatives[6] as well as functionalized cyclic enol ethers.[7]

We wish to report here an unprecedented base-induced anionic sequence involving five different reactions for the flexible and efficient preparation of various cycloheptenes,[8] starting from simple cyclic β-keto esters **1** and **2**[9] and 2-substituted acroleins **3** (Scheme 1).

The success of this new domino reaction is based on the *in situ* selective formation and ring opening of 2-hydroxybicyclo[3.2.1]octanone intermediates that constitute well-known precursors of functionalized seven-membered rings.[10]

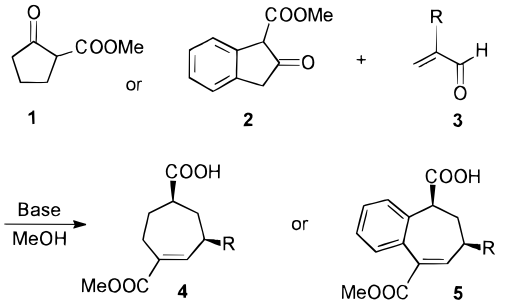
The overall transformation named MARDi cascade involves a Michael addition, an intramolecular aldol condensation, a retro-Dieckmann reaction followed by dehydration, and chemoselective ester saponification. The result is the facile one-pot diastereoselective formation of highly functionalized and synthetically valuable cycloheptenes **4** and **5** bearing two stereogenic centers, a potential Michael acceptor double bond, and two chemically differentiated carboxylate groups (Scheme 1).

Table 1. Effect of Base on the Condensation of 1 with 3a in MeOH

entry	condns[a]	yield[b] (%)
1	KOH, 0.5 equiv, 6 h	39
2	K_2CO_3, 0.5 equiv, 48 h	46
3	DBU,[c] 0.25 equiv, 51 h	32
4	DBU, 0.5 equiv, 47 h	44
5	DBU, 0.25 equiv, 9 h[d]	68
6	KOH, 2.7 equiv, 7 h	73
7	K_2CO_3, 1.5 equiv, 22 h	82
8	DBU, 1 equiv, 18 h	90
9	DBU, 1 equiv, 72 h	76

[a] Room temperature. [b] After acidic workup. [c] DBU: 1,8-diazabicyclo[5.4.0]undec-7-ene. [d] Reflux.

Scheme 1. Domino Reaction Leading to Cycloheptenes 4 and 5



a: R = Me; **b**: R = Et; **c**: R = *n*Bu; **d**: R = Ph; **e**: R = ≡SiMe$_3$

f: R = $(CH_2)_2OBn$; **g**: R = $(CH_2)_2COOMe$

The feasibility of our cascade was first tested with Dieckmann ester **1** and 2-methylpropenal (**3a**) leading to **4a** (Table 1). A search for an efficient base/solvent system revealed that good isolated yields of unsaturated acid **4a** could be reached by employing only a catalytic amount of base such as KOH, K_2CO_3, or 1,8-diazabicyclo-[5.4.0]undec-7-ene (DBU) in MeOH at room temperature (Table 1, entries 1−5). While the overall transformation seems not to be affected by the nature of the base, in one case higher temperature improved the yield to 68% (Table 1, entry 5). On the other hand, an excess of KOH or K_2CO_3 gives synthetically useful yields (Table 1, entries 6 and 7), and after various trials, 1 equiv of DBU at room temperature for 18 h gives the best result leading to **4a** with 90% isolated yield (Table 1, entry 8). Prolonged reaction time results in lower yield owing to partial degradation (Table 1, entry 9).

The method has been applied to several 2-substituted α,β-unsaturated aldehydes, and the results are summarized in Table 2. All reactions are unoptimized but give reproducible results under the standard conditions. Carboxylic acids **4** and **5** are conveniently isolated with high chemical purity by simple acidic workup.[11] Good to excellent yields are obtained regardless of the nature of the substituent (Table 2, entries 1−9), and as expected,[12] in the case of **3e** the reaction proceeds with concomitant C−Si(Me)$_3$ bond cleavage leading to **4e**

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(11) Albeit the chemical purity estimated by NMR (200 and 400 MHz) is always >95%, analytical samples could be obtained by chromatography on Et_3N-deactivated SiO_2. This purification process usually suffers from partial or extensive lost of material by some undetermined degradation process.

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Table 2. Synthesis of Functionalized Cycloheptenes 4 and 5

entry	3	keto ester	t,[a] h	cycloheptene	yield[b]
1	**a**	**1**	18	**4a**	90
2	**b**	**1**	50	**4b**	96
3	**c**	**1**	22	**4c**	75
4	**d**	**1**	19	**4d**	91
5	**e**	**1**	50	**4e**[c]	71
6	**f**	**1**	48[d]	**4f**	87
7	**g**	**1**	48	**4g**	84
8	**a**	**2**	9	**5a**	98
9	**f**	**2**	24	**5f**	62

[a] Unless otherwise noted, all reactions were performed at room temperature in MeOH with 1 equiv of DBU. [b] After acidic workup. [c] R = −C≡CH. [d] Reflux.

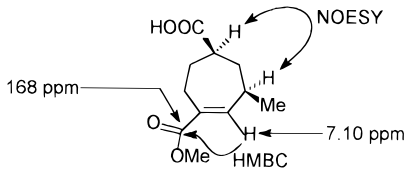


Figure 1. Structure of **4a**.

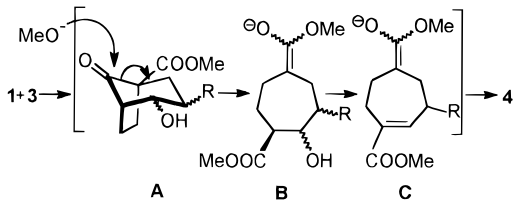
(Table 2, entry 5, R = −C≡CH). Functionalized alkyl chains can also be introduced efficiently at the allylic position (Table 2, entries 6, 7, and 9), giving useful intermediates ready for further inter- or intramolecular synthetic transformations by specific manipulation of the diverse sites of reactivity.[13]

Bicyclic keto ester **2**[9] gives similar results (Table 2, entries 8 and 9) allowing for the facile construction of the corresponding functionalized bicyclo[5.4.0]undecene ring systems found in many natural products.

Cycloheptenes **4** and **5** are obtained with a complete diastereoselectivity, and their structure and stereochemistry have been unambiguously established by extensive NMR studies (Figure 1). Selective irradiations and a NOESY interaction between H_1 and H_3 clearly showed the 1,3-*cis* arrangement. On the other hand, the heteronuclear multibond correlation (HMBC) spectrum revealed a cross-peak due to a $^3J_{C-H}$ coupling constant between the vinyl proton at 7.10 ppm and the carbonyl function (168 ppm) of the conjugated ester, indicating the chemoselective saponification of the nonconjugated ester.[14]

Since it is known that the direct carbocyclization of *β*-keto ester **1** with **3a**, leading to bicyclo[3.2.1]octanes **A** (R = Me) is poorly diastereoselective,[3] it seems more probable that the stereochemistry of this new five-step anionic domino reaction is determined by the stereoselectivity of the proton capture from the last intermediate **C** of the cascade (Scheme 2).[15] Indeed, combination of the higher stability[16] of the 1,3-*cis* orientation of R and COOH groups in cycloheptenes **4** and **5** compared to the 1,3-*trans* isomers and of a sterically controlled protonation from the less hindered face in the common intermediate **C** can argue for the observed diastereoselectivity.

Scheme 2. Diastereoselectivity of the MARDi Cascade



The extremely simple, economical, and environmentally safe experimental conditions associated with the observed diastereoselectivity make this new base-induced domino reaction a synthetically attractive and versatile approach for the rapid construction of highly functionalized cycloheptenes from cyclopentanones. Synthetic exploitation of this stereoselective five-step cascade is now under active investigation.

Acknowledgment. We are very grateful to Dr. R. Faure (UPRESA 6009) for NMR determinations and to Dr. J. M. Pons (UMR 6516) for semiempirical calculations and fruitful discussions. We would like to thank very friendly Dr. P. Crucianni and Prof. M. Malacria from the University of Paris VI (URA 408) for a generous gift of aldehyde **3e**.

Supporting Information Available: Experimental procedure for the preparation of compounds **4** and **5** and spectral data with complete characterization of all new compounds reported herein, including copies of NOESY and HMBC spectra for **4a** (7 pages).

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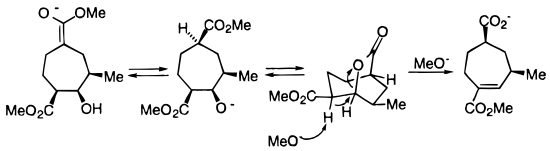
(12) Dickson, R. S.; Kirch, H. P. *Aust. J. Chem.* **1972**, *25*, 1815−1818.

(13) The study of the synthetic utility of these derivatives as potential dienophiles, Michael acceptors, and [3 + 2] cyclopentannulation partners is underway.

(14) The system DBU/MeOH/H_2O has been found to be quite efficient for selective ester saponifications at room temperature, and these results will be disclosed in due course: Filippini, M.-H. Ph.D. Thesis, Marseille, September 1996.

(15) Another mechanism suggested by one of the reviewers involving an intramolecular lactonization/elimination sequence from *β*-hydroxy cycloheptane isomers cannot be ruled out although it could not be effective with α-epimers.



(16) Heats of formation, nicely provided by one of the reviewers and calculated with PCMODEL for both 1,3-*cis* and 1,3-*trans* isomers of **4a**, corroborate our own results obtained from AM1/RHF (AMPAC) semiempirical calculations and showed a preference of only 1−2.2 kcal in favor of the 1,3-*cis*-diequatorial isomer, which corresponds to an approximate 80:20 to 95:5 mixture if thermodynamic equilibrium is achived and cannot argue alone for the complete diastereoselectivity observed.