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The MARDi Cascade: A Michael-Initiated Domino-Multicomponent Approach for the Stereoselective Synthesis of Seven-Membered Rings

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Abstract: The MARDi cascade is a recently invented three-component Michael-initiated condensation involving 1,3-dicarbonyl derivatives. It allows regio- and stereocontrolled access to a variety of functionalised and substituted seven-membered rings. The substitution array can be diastereoselectively modulated by appropriate choice of the reaction partners, and the reaction allows the control of up to five newly created stereocentres and a complete chiral induction in the case of an optically active ketone precursor. The high level of diastereoselectivity observed has been attributed to total thermodynamic control of the reaction. The attractiveness of the present domino three-component approach to seven-membered rings resides in the diversity of carbo- and heterocyclic structures that can be accessed with total regiocontrol and high stereocontrol by starting from simple substrates, under user and environmentally friendly conditions, as now required in modern organic chemistry.

Keywords: domino reactions · Michael addition · multicomponent reactions · seven-membered rings · stereoselectivity

Introduction

The rapid creation of molecular complexity in a regio- and stereodefined manner from simple substrates, combining economical aspects[1,2] with environmental ones,[3] constitutes a great challenge in modern organic chemistry from both academic and industrial points of view. In this field, multicomponent reactions[4] (MCRs) involving domino processes[5] have emerged as powerful tools in diversity-oriented synthesis (DOS) and have found multiple applications in the discovery of new bioactive small molecules.[6] In the field of MCRs, isocyanide-based transformations and metal-catalyzed processes largely lead the way.[4] In our laboratory, there is an ongoing interest in domino and multicomponent reactions that involve 1,3-dicarbonyls and their derivatives.[7] As part of this program, we discovered a new anionic domino three-component two-carbon ring expansion for the stereoselective preparation of functionalised seven-membered rings[8,9] that we named MARDi (an acronym for Michael-aldol–retro-Dieckmann) cascade. The development of new approaches to substituted stereodefined cycloheptanes constitutes a worthwhile synthetic pursuit because of their ubiquitousness in naturally occurring products and their usefulness as synthetic building blocks.[10] In this article, we report the full detailed study of the MARDi cascade.

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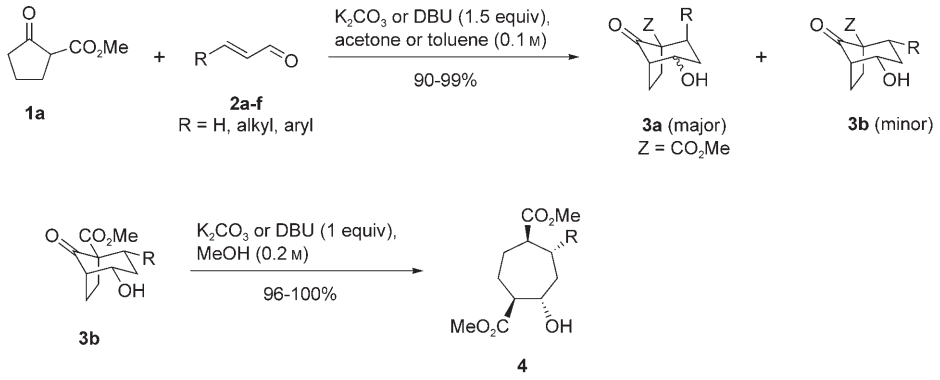
Results and Discussion

The MARDi cascade with β-ketoesters: The discovery of the MARDi cascade came out from a previous study on the synthesis and reactivity of 2-hydroxybicyclo[3.2.1]octan-8-ones.[11] The reaction of the Dieckmann ester **1a** with acrolein (**2a**) or various β-substituted α,β-unsaturated aldehydes **2b–f** in the presence of base (1.5 equiv of K_2CO_3 or 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU)) in acetone or toluene gives the substituted 2-hydroxybicyclo[3.2.1]octan-8-ones **3** by a domino Michael addition–intramolecular aldol cyclisation (Scheme 1). The bicyclic products **3** are generally obtained in high yields and with moderate diastereoselectivities. A study on the reactivity of these 2-hydroxybicyclo-[3.2.1]octan-8-ones, pioneered by Stork–Landesman[12] and Buchanan,[13] revealed that substituted cycloheptanols could be obtained stereoselectively by a retro-Dieckmann fragmentation (i.e. **3b**→**4**) promoted by K_2CO_3 or DBU (1.0 equiv) in methanol (Scheme 1).[14] This two-step synthesis of substituted cycloheptanols prompted us to surmise



Scheme 1. Synthesis and reactivity of 8-oxo-bicyclo[3.2.1]octanols.

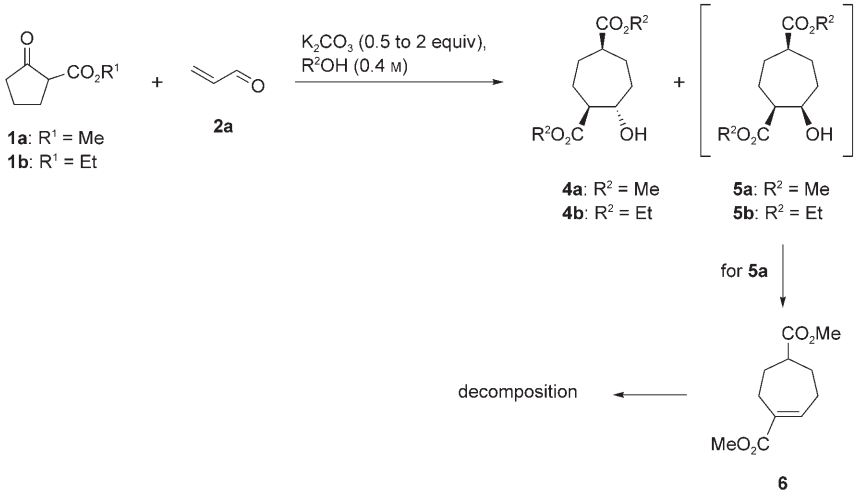
that the overall cascade Michael addition–regioselective aldol cyclisation–retro-Dieckmann fragmentation would be possible in a one-pot process by starting from the Dieckmann ester **1a** and α,β-unsaturated aldehydes **2** in MeOH as the third component. Indeed, we were pleased to observe that the cycloheptanol **4a** was obtained stereoselectively in 36% yield (together with very polar material) from the Dieckmann ester **1a** and acrolein (**2a**, 1.5 equiv) in the presence of two equivalents of K_2CO_3 in methanol (0.4 M) by means of the MARDi cascade (Scheme 2, Table 1, entry 1).[15] A very small amount of the unstable cycloheptene **6** was also detected but could not be isolated. The structure of cycloheptanol **4a** has been confirmed by perfect matching of its NMR spectroscopic data with those obtained previously in the two-step synthesis of the same product.[11] When the same reaction was performed with a substoichiometric amount of K_2CO_3 (0.5 equiv), the diastereomeric cycloheptanols **4a** and **5a** (dr = 1.5:1) were obtained in 94% yield (entry 2). These results suggest that in the presence of an excess of base, the all-*cis* cycloheptanol **5a** undergoes dehydration to the cycloheptene **6**, which decomposes rapidly in the reaction mixture (Scheme 2). The less expensive Dieckmann ethyl ester **1b** can also be used in this reaction with the same efficiency to provide the di(methylcarboxylate)cycloheptanols **4a** and **5a** (dr = 1.5:1), following a total transesterification, if the reaction is conducted in methanol (entry 3). As expected, the reaction in ethanol provides the di(ethylcarboxylate)cycloheptanols **4b** and **5b** (dr = 1.5:1) in slightly lower yield, probably as a result of the higher steric hindrance of the alkoxide nucleophile in the final retro-Dieckmann step (entry 4).

Table 1. The MARDi cascade with the Dieckmann esters **1a**,**b** and acrolein (**2a**).

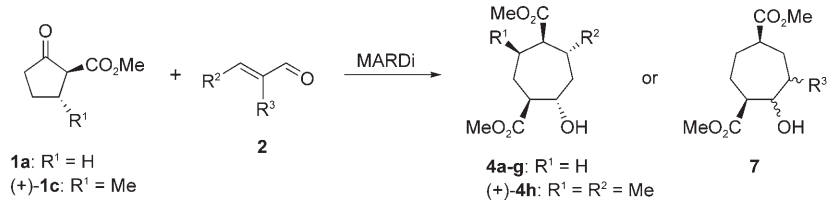
Entry	Substrate	Conditions[a]	Product	Yield [%][b]
1	**1a**	K_2CO_3 (2.0 equiv), MeOH (0.4 M)	**4a**	36
2	**1a**	K_2CO_3 (0.5 equiv), MeOH (0.4 M)	**4a/5a** 1.5:1	94
3	**1b**	K_2CO_3 (0.5 equiv), MeOH (0.4 M)	**4a/5a** 1.5:1	95
4	**1b**	K_2CO_3 (0.5 equiv), EtOH (0.4 M)	**4b/5b** 1.5:1	84

[a] All reactions were conducted at room temperature with 1.5 equiv of acrolein (**2a**). [b] Yield of isolated product.

We next turned our attention to the synthesis of more-substituted cycloheptanols by using substituted acroleines and substituted 2-oxo-cyclopentanecarboxylate methyl esters (Scheme 3). The condensation between the Dieckmann ester **1a** and crotonaldehyde (**2b**) was chosen for the optimisation study (Table 2). Under the conditions previously developed for the condensation of acrolein (0.5 equiv of K_2CO_3), the expected substituted cycloheptanol **4c** was obtained diastereoselectively (dr > 25:1) in 54% yield (entry 1). Increasing the quantity of base and the use of a chelating additive had no effect on both the yield and diastereoselectivity (entries 2 and 3). Magnesium carbonate left the starting material unchanged (entry 4), while cesium carbonate allowed the formation of **4c** in modest yield (entry 5), and the use of a chelating additive resulted in the decomposition of the products, even at low temperature (entries 6 and 7). Alternatively,



Scheme 2. The MARDi cascade with the Dieckmann esters **1a**,**b** and acrolein (**2a**).



Scheme 3. The MARDi cascade: synthesis of cycloheptanols.

Table 2. Optimization study for the MARDi cascade with the Dieckmann ester **1a** and crotonaldehyde (**2b**).

Entry	Conditions[a]	Yield of **4c** [%][b]
1	K_2CO_3 (0.5 equiv), 20 h	54
2	K_2CO_3 (1 equiv), 21 h	54
3	K_2CO_3 (1 equiv), [18]crown-6, 23 h	54
4	$(MgCO_3)_4{\cdot}Mg(OH)_2{\cdot}5H_2O$, (1 equiv), 18 h	no reaction
5	Cs_2CO_3 (1 equiv), 18 h	37
6	Cs_2CO_3 (1 equiv), [24]crown-8, 20 h	decomposition
7	Cs_2CO_3 (1 equiv), [24]crown-8, −20 °C, 20 h	decomposition
8	MeONa (1 equiv), 48 h	63
9	KOH (1 equiv), 27 h	74
10	pyridine (1 equiv), 96 h	no reaction
11	DABCO (1 equiv), 23 h	0[c]
12	NEt_3 (1 equiv), 28 h	0[c]
13	DMAP (1 equiv), 72 h	0[c]
14	TMG (0.5 equiv), 26 h	49
15	TMG (1 equiv), 26 h	48
16	DBN (0.5 equiv), 96 h	52
17	DBU (0.5 equiv), 26 h	50
18	DBU (1 equiv), 26 h	94
19	DBU (2.0 equiv), 26 h	52
20	DBU (1.0 equiv), pyridine (1 equiv), 26 h	78
21	DBU (1.0 equiv), HMPA (25% vol), 22 h	32

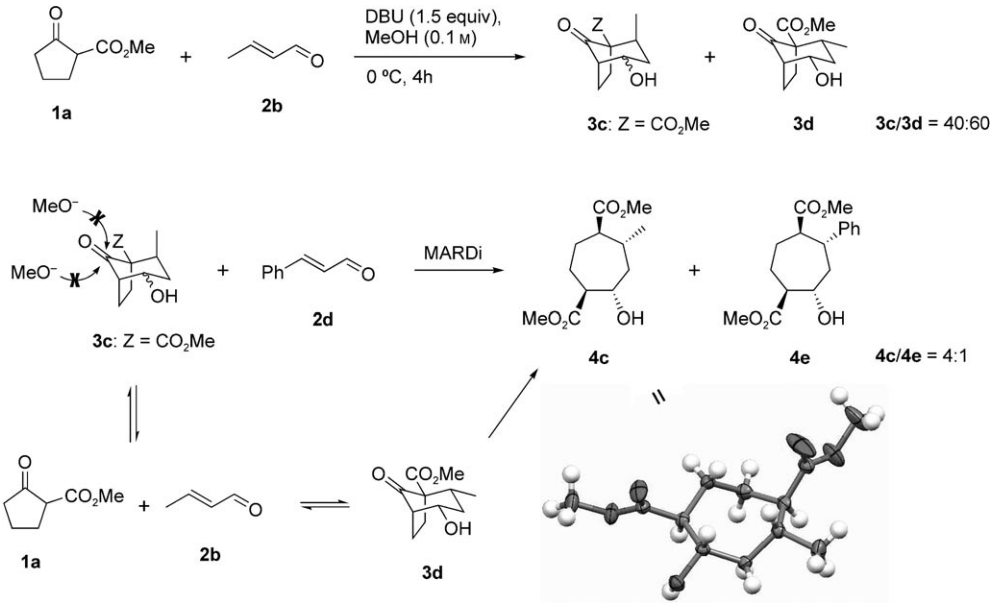
[a] Unless otherwise mentioned, all reactions were conducted in dry MeOH (0.4 M) at room temperature with 1.5 equiv of crotonaldehyde (**2b**). [b] Except for entries 1 and 18 in which **4c** was isolated by flash chromatography, yields were determined from the ^1H and/or ^{13}C NMR spectra of the crude mixtures (dr > 25:1). [c] The bicyclo[3.2.1]octanols **3a** and **3b** (R = Me) were isolated (dr = 1:1.5).

sodium methoxide and potassium hydroxide proved superior to potassium carbonate (entries 8 and 9). Non-ionic bases such as pyridine left the starting material unchanged even after a prolonged reaction time (entry 10), and 1,4-diazabicyclo[2.2.2]octane (DABCO), triethylamine or 4-dimethylaminopyridine (DMAP) resulted in the formation of the corresponding bicyclo[3.2.1]octanols **3a** and **3b** (R = Me, entries 11–13, respectively). On the other hand, tetramethylguanidine (TMG), 1,5-diazabicyclo[4.3.0]non-5-ene (DBN, after a prolonged reaction time) and DBU gave the desired cycloheptanol **4c** with a comparable efficiency to K_2CO_3 (entries 14–17). Finally, 1.0 equiv of DBU was found to be efficient to give **4c** in high yield and with very good diastereoselectivity (dr > 25:1, entry 18), while an excess of DBU or additives had a deleterious impact on the yield (entries 19–21), probably favouring the dehydration of the cycloheptanol to the corresponding unstable cycloheptene as in the case of acrolein.

The structure of **4c** has been deduced from the strong NOEs observed in NOEDIFF experiments between the protons α to the methyl, the hydroxyl (1,3-*cis* for the methyl and the hydroxyl groups) and the two carboxyl groups (1,4-*cis* for the two carboxylates). The 1,2-*trans* relationship between the hydroxyl and the methylcarboxyl groups was deduced from the large $^3J(H,H)$ coupling constant (10 Hz) observed between the protons α to these substituents. The structure of **4c** was secured later by X-ray diffraction analysis (Scheme 4).[16]

With an efficient protocol for the stereoselective synthesis of the substituted cycloheptanol **4c** in hand, we explored the scope of the MARDi cascade, first, with a variety of β-substituted acroleines. The results are summarized in Table 3. It appears that the MARDi cascade is a general reaction that can be performed in good to high yield with alkyl (entries 1,2) and aryl (entries 3–5) β-substituted aldehydes with excellent diastereoselectivity. By starting from the optically active 5-methyl-2-oxo-cyclopentanecarboxylate methyl ester (+)-**1c** derived from (+)-pulegone,[17] the MARDi cascade with crotonaldehyde (**2b**) provided the optically active cycloheptanol (+)-**4h**, which contains five stereogenic centres, with total chiral induction (entry 6).

The excellent diastereoselectivity observed for the synthesis of cycloheptanols **4c**–**h** by the MARDi cascade is in sharp contrast with the low selectivities observed for the preparation of the intermediate bicyclo[3.2.1]octanones **3** from the same substrates. The interrupted reaction of the Dieckmann ester **1a** with crotonaldehyde (**2b**) in the presence of 1.5 equivalents of DBU in methanol at 0 °C for 4 h gave the methyl 2-hydroxy-4-methyl-8-oxo-bicyclo-[3.2.1]octanecarboxylates (**3c** and **3d**) in good yield, but as a 40:60 mixture of epimers at C4 (Scheme 4).[11] The high diastereoselectivity of the MARDi cascade can thus only be explained by the selective retro-Dieckmann fragmentation of the equatorial 4-methyl bicyclo[3.2.1]octanone **3d** to give the expected cycloheptanol **4c**, while the axial 4-methyl bicyclo[3.2.1]octanone **3c** (kinetic product, see the Supporting Information) suffered a tandem retro-aldol–retro-Michael ring opening to give back **1a** and **2b**, followed by a thermodynamically controlled ring reconstitution that led to equatorial 4-methylbicyclo[3.2.1]octanone **3d**, precursor of the cycloheptanol **4c**. Evidence for total thermodynamic control of the MARDi cascade came from a cross experiment in the presence of cinnamaldehyde (**2d**). Indeed, when the axial 4-methylbicyclo[3.2.1]octanone **3c** is allowed to react with cinnamaldehyde (**2d**) under the optimised MARDi cascade conditions for β-substituted aldehydes, a mixture of cycloheptanols **4c** (40%) and **4e** (10%) is obtained, accompanied by unreacted **3c** (Scheme 4). This specific behaviour can be rationalised by invoking the steric hindrance of the axial methyl substituent on the β-face



Scheme 4. The diastereoselectivity of the MARDi cascade with aldehydes **2b–f**.

Table 3. The MARDi cascade with β-substituted acroleines.[a]

Entry	Substrate	Aldehyde	Product	Yield [%][b]
1	**1a**	**2b**: R^2=Me	**4c**: R^1=H, R^2=Me	94
2	**1a**	**2c**: R^2=*n*Pr	**4d**: R^1=H, R^2=*n*Pr	60
3	**1a**	**2d**: R^2=Ph	**4e**: R^1=H, R^2=Ph	96
4	**1a**	**2e**: R^2=2-furyl	**4f**: R^1=H, R^2=2-furyl	64
5	**1a**	**2f**: R^2=*o*-anisyl	**4g**: R^1=H, R^2=*o*-anisyl	83
6	(+)-**1c**	**2b**: R^2=Me	(+)-**4h**: R^1=R^2=Me	43

[a] All reactions were conducted at room temperature in dry MeOH (0.3–0.4 M) by using 1 equiv of DBU and 1.5 equiv of aldehyde. [b] Yields are given for the isolated homogeneous products obtained after silica-gel flash chromatography.

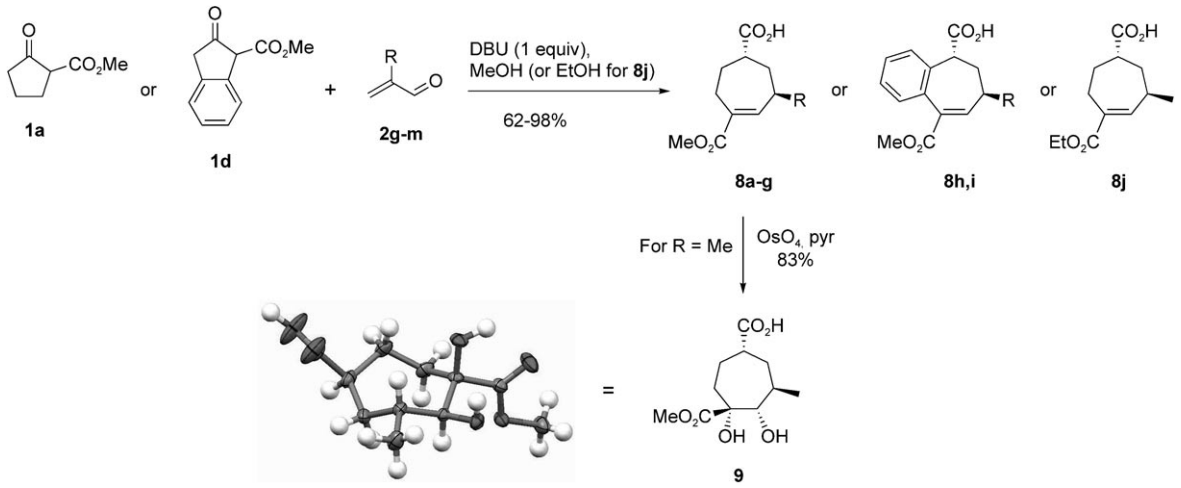
which prevents the retro-Dieckmann fragmentation. Finally, for the optically active pentasubstituted cycloheptanol **4h** obtained from crotonaldehyde (**2b**), the initial Michael addition step occurs with high diastereofacial control as a result of the presence of the 3-methyl substituent in the β-ketoester **1c**. This results in the exclusive 1,3-*trans* relationship between the two methyl substituents in the cycloheptanol (+)-**4h**.

With α-substituted acroleines (no β-substituent), the issue of the MARDi cascade is somewhat different. In early experiments, the cycloheptanols **7** (R^3=Me) could be obtained from the Dieckmann ester **1a** and methacrolein (**2g**), but in moderate yield (36% with 0.5 equiv of K_2CO_3) and with poor diastereoselectivity as a result of the lack of control over the newly created stereocentre which is formed during the Michael addition (Scheme 3). A brief study aiming at optimising the nature and amount of base established that cycloheptanols **7** could not be obtained in a yield higher than 40% and, more importantly, that increasing the amount of base resulted in dramatic drop of the yield (e.g. <5% with 1.0 equiv DBU). However, the crude mixtures were clean, containing essentially the cycloheptanols **7**, which prompted us to examine the content of the aqueous layer. After acidification with HCl and extraction with diethyl ether or ethyl acetate, we were pleased to isolate the clean, diastereomerically pure, cycloheptenic acids **8** in good to high yield.[18] The acid **8a** was selected for the optimisation study (Table 4) and one equivalent of DBU in 0.4 M methanol was found to give the best result (entry 9, Scheme 5). While the overall transformation is not much affected by the nature of the base (compare entries 2, 5 and 9), prolonged reaction times result in lower yields,

Table 4. Optimization study for the MARDi cascade between the Dieckmann ester **1a** and methacrolein (**2g**).

Entry	Conditions[a]	Yield of **8a** [%][b]
1	K_2CO_3 (0.5 equiv), 48 h	46
2	K_2CO_3 (1.5 equiv), 22 h	82
3	KOH (0.5 equiv), 6 h	39
4	KOH (1 equiv), 17 h	65
5	KOH (2.7 equiv), 7 h	73
6	DBU (0.25 equiv), 51 h	32
7	DBU (0.5 equiv), 9 h, reflux	60
8	DBU (0.5 equiv), 47 h	44
9	DBU (1.0 equiv), 18 h	90
10	DBU (1.0 equiv), 72 h	76
11	DBU (2.0 equiv), 24 h	62[c]

[a] Unless otherwise mentioned, all reactions were conducted in MeOH (0.3–0.4 M) at room temperature with 1.5 equiv of aldehyde. [b] Yields are given for the clean homogeneous, diastereomerically pure, crude products obtained after acidic workup. [c] 18% of the corresponding diacid was also present in the crude mixture.



Scheme 5. The MARDi cascade with aldehydes **2g–m**.

owing to partial decomposition (entry 10), and an excess of DBU results in partial double saponification to provide a substantial amount of the corresponding diacid (entry 11). A variety of α-substituted acroleines were tried, and the results are summarised in Table 5. Good to excellent yields were obtained regardless of the nature of the substituent, and functionalised alkyl chains can be introduced (entries 6, 7, and 9). As expected,[19] in the case of aldehyde **2k**, the reaction proceeds with concomitant C–$SiMe_3$ bond cleavage leading to **8e** (entry 5). The bicyclic β-ketoester **1d** gave similar results (entries 8 and 9), allowing the facile construction of the corresponding functionalised bicyclo[5.4.0]undecene ring system found in many natural products. When performing the reaction in ethanol and starting from **1a** and methacrolein (**2g**), an additional *trans*-esterification occurred to give the corresponding ethyl ester **8j** (entry 10).

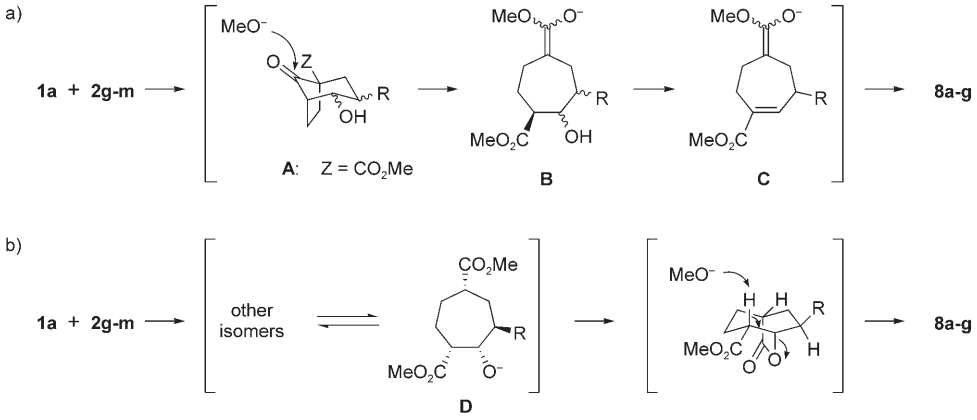
Table 5. The MARDi cascade with α-substituted acroleines.[a]

Entry	Substrate	Aldehyde	t [h]	Product	Yield [%][b]
1	**1a**	**2g**: R = Me	18	**8a**: R = Me	90
2	**1a**	**2h**: R = Et	50	**8b**: R = Et	96
3	**1a**	**2i**: R = *n*Bu	22	**8c**: R = *n*Bu	75
4	**1a**	**2j**: R = Ph	19	**8d**: R = Ph	91
5	**1a**	**2k**: R = C≡CSiMe_3	50	**8e**: R = C≡CH	71
6	**1a**	**2l**: R = $(CH_2)_2$OBn	48[c]	**8f**: R = $(CH_2)_2$OBn	87
7	**1a**	**2m**: R = $(CH_2)_2CO_2$Me	48	**8g**: R = $(CH_2)_2CO_2$Me	84
8	**1d**	**2g**: R = Me	9	**8h**: R = Me	98
9	**1d**	**2l**: R = $(CH_2)_2$OBn	24	**8i**: R = $(CH_2)_2$OBn	62
10	**1a**	**2g**: R = Me	96[d]	**8j**	80

[a] Unless stated otherwise, all reactions were conducted at room temperature in dry MeOH (0.4 M) by using 1.0 equiv of DBU and 1.5 equiv of aldehyde. [b] Yields are given for the clean homogeneous, diastereomerically pure, crude products obtained after acidic workup. [c] Reflux. [d] Reaction performed in dry EtOH.

The cycloheptenes **8a–j** are obtained with excellent diastereoselectivity, and their structure has been determined by extensive NMR spectroscopic studies. The NOESY spectrum of **8a** clearly shows a correlation spot between the Me group (d, $\delta = 1.20$ ppm) and the hydrogen atom α to the COOH ($\delta = 2.84$ ppm), indicating that they are on the same face of the seven-membered ring (1,3-*trans* relationship between Me and COOH). The HMBC spectrum revealed a crosspeak as a result of a ^3J(C,H) coupling constant between the vinyl proton ($\delta = 7.10$ ppm) and the carbon atom of the conjugated ester ($\delta =$ 168.6 ppm), indicating that chemoselective saponification of the non-conjugated ester had occured. The structure of **8a** has recently been confirmed by X-ray diffraction analysis of the dihydroxylated derivative **9** obtained in 83% yield from **8a** (Scheme 5).[16]

Our previous work on the synthesis of bicyclo[3.2.1]octanes **A** (Scheme 6) from the Dieckmann ester **1a** and methacrolein (**2g**) showed that this carbocyclisation was poorly diastereoselective,[11] and no steric argument can be used here for the chemoselective retro-Dieckmann fragmentation of one isomer of **A**. Thus, during the reaction, the cycloheptanols **B** are formed as a mixture of isomers, as proven by our initial attempts on this reaction (see above). One can then postulate that a stereoselective proton capture of the putative last intermediate **C** of the cascade occurs, followed by chemoselective saponification of the non-conjugated ester with the water produced on dehydration or upon hydrolysis of the reaction mixture (Scheme 6a). However, thermodynamic considerations cannot account for the 1,3-*trans* diastereoselectivity observed for the MARDi cascade with α-substituted aldehydes, the 1,3-*trans* cycloheptenic acids **8** being the less-stable isomers, as corroborated by simple theoretical calculations.[20] Furthermore, when the reaction of entry 1 (Table 5) is run in the presence of 3 Å molecular sieves, the



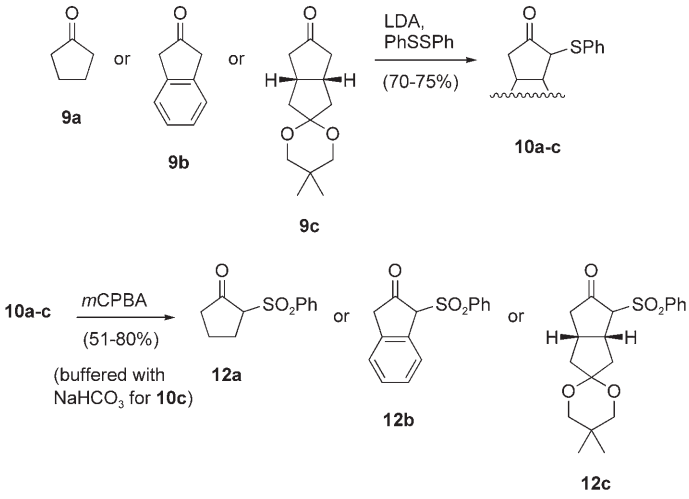
Scheme 6. The diastereoselectivity of the MARDi cascade with aldehydes **2g–m**.

cycloheptenic acid **8a** is isolated in 80% yield, indicating that the presence of water is not necessary for the saponification step. Therefore, the high diastereoselectivity and the regioselective saponification might be better explained by invoking an intramolecular lactonization–elimination sequence of the isomer **D** which drives the equilibrium, resulting only in the formation of the 1,3-*trans* cycloheptenic acids **8** (Scheme 6b).

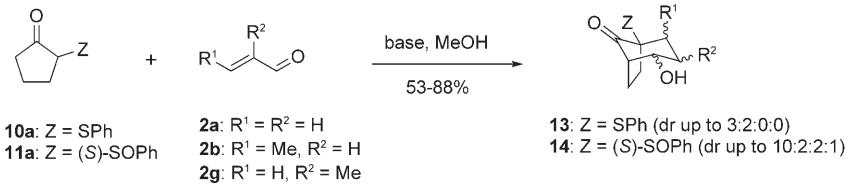
The MARDi cascade with β-ketosulfones: To further expand the scope of the MARDi cascade, we studied its feasibility with easily accessible thiofunctionalised precursors.[21] The sulfides **10a–c**[22] were prepared by using modified Trost conditions[23] (1,3-dimethyl-3,4,5,6-tetrahydro-2(1*H*)-pyrimidinone (DMPU) advantageously replaces hexamethylphosphoramide (HMPA)), the optically active sulfoxide **11a** (mixture of two diastereomers) was prepared from the cyclopentanone *N*-phenylimine and (−)-menthyl *p*-toluenesulfinate[24] and the sulfones **12a–c** were obtained by oxidation of the corresponding sulfides with *meta*-chloroperbenzoic acid (*m*CPBA, Scheme 7).[25]

Preliminary experiments showed that in the presence of base (K_2CO_3 or DBU) and methanol, β-ketosulfide **10a** reacts with α,β-unsaturated aldehydes **2a**,**b**,**g** to give the 8-oxo-bicyclo[3.2.1]octanols **13** in good yields and with low stereoselectivities (Scheme 8). The final retro-Dieckmann step of the MARDi cascade does not occur, probably due to a lack of stabilization of the negative charge on the carbon atom that bears the sulfide group. The same reactivity was observed with the optically active β-ketosulfoxide **11a** with slightly better stereoselectivity.

We next examined the reaction of the β-ketosulfone **12a** with representative α,β-unsaturated aldehydes and were pleased to find that sulfonyl-substituted cycloheptanols could be obtained stereoselectively by means of the MARDi cascade (Table 6). After an optimisation study, we found that 1) DBU is not satisfactory in the case of β-ketosulfones, leaving substantial amounts of the intermediate bicyclo[3.2.1]octane unfragmented, 2) a stoichiometric amount of K_2CO_3 gives the best result in most cases and 3) dilution of the reaction mixture and addition of a co-solvent (THF or toluene), which prevents the direct retro-Dieckmann cleavage of the starting material, has a pronounced beneficial impact on both the yield and the selectivity. Indeed, under the optimised conditions (1.0 equiv K_2CO_3, 1:1 THF/methanol, 0.06 M, RT, 20 h), the reaction of β-ketosulfone **12a** with acrolein (**2a**) yields 93% of the sulfonyl cycloheptanol **15a** as a 5:1 inseparable diastereomeric mixture (entry 1). The same reaction conducted with crotonaldehyde (**2b**) provides, stereoselectively, the corresponding substituted cycloheptanol **15b** in high yield (entry 2). In the case of 2-substituted aldehydes, such as methacrolein (**2g**) and 2-butyl acrolein (**2i**), the corresponding cycloheptanols **15c** and **15d** are also obtained stereoselectively (entries 3 and 4, respectively), but together with various amounts of the corresponding carboxylic acids. The saponifi-

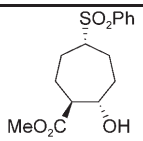
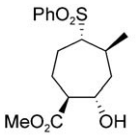
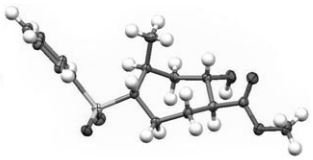
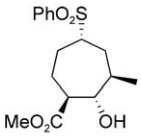
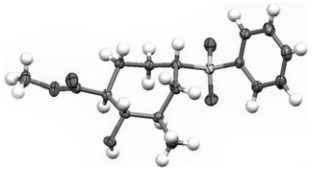
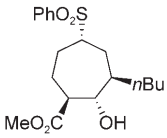
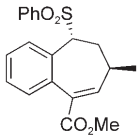
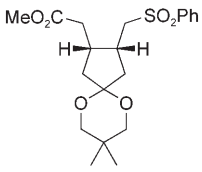


Scheme 7. Thiofunctionalised precursors tested in the MARDi cascade.



Scheme 8. Reactivity of β-keto-sulfides and -sulfoxides.

Table 6. The MARDi cascade with β-ketosulfones.[a]

Entry	Substrate	Aldehyde	Product[b]	Yield [%][c] (major)	dr[d]
1	**12a**	**2a**	 **15a**	93	5:1
2	**12a**	**2b**	 =  **15b**	90 (51)	4:1:1:1
3[e]	**12a**	**2g**	 =  **15c**	95 (62)	8:2:1:1
4	**12a**	**2i**	 **15d**	99 (79)	8:1:1
5	**12b**	**2g**	 **15e**	73 (40)	2:1
6	**12c**	**2a**,**b**	 **16**	nd[f]	

[a] Unless otherwise stated, reactions were performed with 1.5 equiv of aldehyde and 1 equiv of K_2CO_3 in 1:1 MeOH/THF (0.06 M) at room temperature for 20 h. [b] The represented diastereomer is the major product. [c] Yields are given for the clean crude mixture of diastereomers. Yields in parenthesis are given for the isolated major diastereomers obtained by single recrystallisation for **15b**, **15c** and **15e**, or silica gel flash chromatography for **15d**. [d] Diastereomeric ratios were determined from the crude ^1H and ^{13}C NMR spectra. [e] Reaction performed with 2 equiv of K_2CO_3. [f] nd = not determined. The reaction was monitored by mass spectroscopy (ESI+).

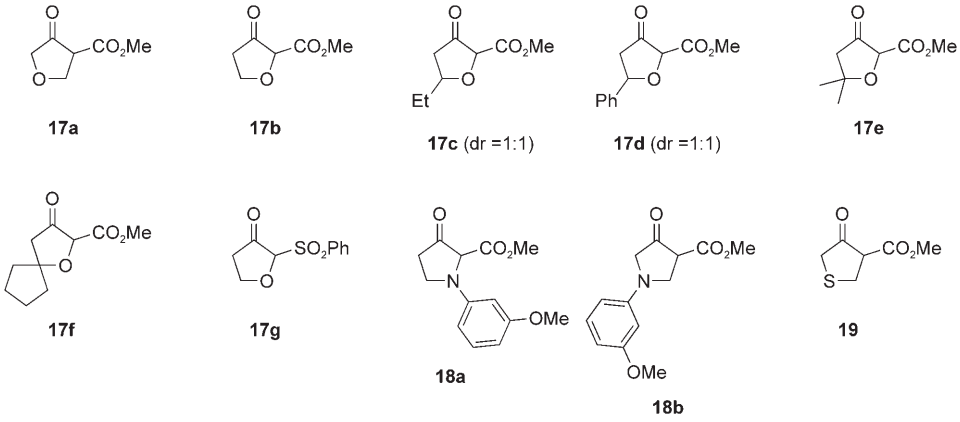
cation probably occurred upon hydrolysis of the reaction, and the acids were converted back to the methyl esters by treatment with (trimethylsilyl)diazomethane prior to isolation.[26] The MARDi cascade can also be performed with the bicyclic β-ketosulfone **12b**, which reacts with methacrolein (**2g**) to provide, stereoselectively, the bicyclo[5.4.0]undecane **15e** (entry 5). In this case, the dehydration of the intermediate cycloheptanol seems to be facilitated by the homobenzylic position of the hydroxyl group, leading to a thermodynamically stable conjugated system. However, by starting from the bicyclic β-ketosulfone **12c**, the retro-Dieckmann fragmentation of the starting material was the only reaction observed to give **16**, probably due to the favourable steric strain release compared to the highly demanding formation of the corresponding bridged intermediate (entry 6).

Although the MARDi cascade is less diastereoselective in the sulfonyl series, the diastereomerically pure major isomers could be isolated (except for entry 1) by a very efficient recrystallisation in most cases. The relative configurations of the sulfonyl cycloheptanols **15a–d** and cycloheptene **15e** have been determined by standard high-field 2D NMR spectroscopic techniques and the structures of **15b** and **15c** have been secured by X-ray diffraction analysis.[16] The comparison of the products of the MARDi cascade in the sulfonyl and the corresponding carboxyl series (vide supra) highlights that stereocontrol and chemical differentiation of the final cycloheptane might be achieved by appropriate choice of the stabilising group on the starting cyclopentanone (compare, for example, compounds **4c** with **15b**, and **8a** with **15c**).

The retro-Dieckmann fragmentation is easier for a β-ketophenylsulfone than for a β-ketomethylester (the proton α to a phenylsulfonyl group is about 1.5 pKa units lower than the same proton α to a methyl ester group).[27] This can argue for an easier fragmentation of the intermediate sulfonyl-substituted bicyclo[3.2.1]octane of the MARDi cascade. Thus, the diastereomeric ratio of the alkyl and hydroxyl substituents in cycloheptanol **15b** approximately reflects the diastereomeric ratio of the corresponding intermediate bicyclo[3.2.1]octane (axial methyl at C4 major), the relative configuration of the sulfonyl-substituted carbon atom probably results from a final thermodynamically controlled protonation. In the case of 2-substituted aldehydes, the above mentioned intramolecular lactonization–elimination mechanism (Scheme 6b), which provides evidence for the complete diastereoselectivity observed in the β-ketoester series, cannot be invoked here and thus the seven-membered rings **15c–e** are also obtained as mixtures of isomers.

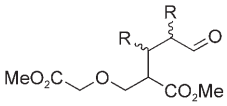
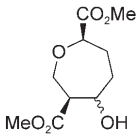
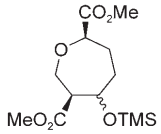
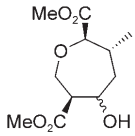
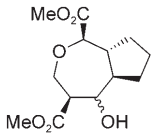
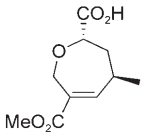
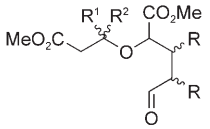
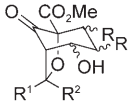
The MARDi cascade in the heterocyclic series: Heterocyclic seven-membered rings constitute the core or a key fragment of a number of bioactive compounds, many of which are isolated from natural sources.[28] The known biological properties of these compounds and the huge potential in drug discovery of this nuclei renders desirable the development of simple and general methodologies for their regio- and stereoselective synthesis. Although the preparation of thiepanes is less documented, the number of methodologies made available for the preparation of azepanes and oxepanes has steadily increased in the past decades.[29] From our previous results, we surmised that the MARDi cascade could allow a quick access to a variety of heterocyclic seven-membered rings.[30]

The hetero-MARDi cascade was first tested (see structures depicted below) in the oxygen series with furanone **17a**, obtained from methyl glycolate and methyl acrylate,[31] and the isomeric furanones **17b–g**, formed by rhodium-carbenoid insertion into the OH bond of the corresponding δ-hydroxy-β-ketoesters[32] or δ-hydroxy-β-ketosulfone[33]. The



study was initiated with furanone **17a** and the representative aldehydes **2a**,**b** and **2g**, which were allowed to react under the previously optimised conditions. The desired oxepane could not be obtained, and the open-chain products of type **20**, resulting from a Michael addition–retro-Dieckmann fragmentation sequence, were the only products isolated (Table 7, entry 1). In this case, the intramolecular aldolisation does not occur due to the presence of the oxygen atom α to the aldolisation site destabilizing the enolate, thus setting the stage for the fragmentation.[34] Further experimental evidence for this explanation came from our trials to synthesise the corresponding bicyclo[3.2.1]octanones (K_2CO_3 or DBU in acetone or THF) which resulted only in the formation of the Michael adduct (no ring-closing aldolisation) even after a prolonged reaction time. We next examined the reactivity of the isomeric furanone **17b** in the MARDi cascade, and were pleased to find that the expected oxepanes could be obtained stereoselectively. The reactions were conducted at various concentrations and a substoichiometric amount of K_2CO_3, again, proved to be the most efficient base for the transformation, giving the best yields in a relatively diluted medium. Actually, these cycloheptanols are relatively unstable in the reaction mixture, particularly in concentrated basic media. For example, at a concentration higher than 0.2 M, the furanone **17b** reacted with acrolein (**2a**) to give the corresponding hydroxyoxepanes **21a** in very low yield as a 1.5:1 mixture of epimers (entry 2). Lowering the concentration to 0.1 and 0.04 M (entries 3 and 4) had no effect on diastereoselectivity, but allowed the formation of **21a** in 24 and 46% yields, respectively. Unfortunately, this compound suffered degradation upon silica-gel chromatography and only a small quantity of **21a** could be isolated. Thus, the crude product **21a** was silylated prior to purifica-

Table 7. The MARDi cascade for the preparation of oxepanes.[a]

Entry	Substrate	Aldehyde	Product[b]	Yield [%][c]
1[d]	**17a**	**2a**,**b**,**g**	 **20**: R = H, Me	nd[n]
2[e]	**17b**	**2a**	 **21a**[f]	14
3[g]	**17b**	**2a**	**21a**	24
4[h]	**17b**	**2a**	**21a**	46
5[h]	**17b**	**2a**	 **21b**[f]	42
6[i]	**17b**	**2b**	 **21c**[j]	28
7[i]	**17b**	**2n**	 **21d**[k]	21
8[l]	**17b**	**2g**	 **21e**[m]	42
9[d]	**17c**–**f**	**2a**,**b**,**g**	 **22**: (R^1 = Et, Ph and R^2 =H) or $R^1 = R^2$ = Me or R^1,R^2 = $(CH_2)_4$ R = H, Me  **23**: (R^1 = Et, Ph and R^2 =H) or $R^1 = R^2$ = Me or R^1,R^2 = $(CH_2)_4$ R = H, Me	nd[n]

[a] Unless stated otherwise, all reactions were performed in dry MeOH (0.04 M) with 1.5 equiv of aldehyde at room temperature for 20 h. [b] For **21a**–**d**, the major isomer is the thermodynamically favoured isomer (α-OH). The relative configurations of compounds **21b**–**e** have been established by 2D NMR spectroscopic techniques. [c] Isolated, except for entries 2–4 for which the yields were estimated from the crude ^{1}H and ^{13}C NMR spectra. [d] K_2CO_3 or DBU (0.5 or 1 equiv). [e] K_2CO_3 (0.25 M, 0.5 equiv). [f] dr = 1.5:1. [g] K_2CO_3 (0.1 M, 0.5 equiv). [h] K_2CO_3 (0.5 equiv). [i] DBU (1 equiv). [j] dr = 6:1. [k] dr = 4:1. [l] DBU (0.5 equiv). [m] dr ≥ 10:1. [n] nd = not determined. The reaction was monitored by mass spectroscopy (ESI+).

tion, allowing the isolation of the corresponding silyl ethers **21b** in 42% yield (dr = 1.5:1) from **17b** (entry 5). This encouraging result prompted us to study the evolution and the diastereoselectivity of the reaction with substituted aldehydes. In this case, DBU gave the best results under the optimised concentration conditions. The reaction of furanone **17b** with crotonaldehyde (**2b**) gave the expected substituted hydroxyoxepanes **21c** (dr = 6:1, Table 7, entry 6). Also, the reaction of **17b** with cyclopentene carboxaldehyde (**2n**) gave the corresponding fused bicyclic compounds **21d** (dr = 4:1, entry 7) stereoselectively with an all-*trans* relationship of five contiguous stereogenic carbon atoms. By analogy with the carbocyclic version of the MARDi cascade, the reaction of **17b** with methacrolein (**2g**) provided the 1,3-*trans* carboxylic acid **21e** in 42% yield with high diastereoselectivity (dr ≥ 10:1, entry 8). In this case, the diastereoselectivity is not as high as in the parent carbocyclic reaction. This result indicates that at least a fraction of the all-*cis* diastereomer of the intermediate dimethyl ester oxepanol also undergoes the intramolecular lactonization–dehydration sequence (see Scheme 6b) to give a very minor amount of the diastereomeric 1,3-*cis* oxepine carboxylic acid, which could not be separated from the major 1,3-*trans* isomer. The rest of the material is essentially composed of degradation products, but trace amounts of the unfragmented bicyclo[3.2.1]octanols, the dimethyl ester oxepanols and the dimethyl ester oxepine could also be detected by mass spectroscopy. Our attempts to synthesize highly substituted oxepanes from the substituted furanones **17c–f** only resulted in the formation of the Michael–retro-Dieckmann products **22** and/or the bicyclo[3.2.1]octanols **23**, together with considerable amounts of degradation products (entry 9). To explain this behaviour, one can argue that the nucleophilic attack of the methoxide anion on both faces of the ketone in the intermediate bicyclo[3.2.1]octanone is sterically disfavoured. Thus the retro-Dieckmann fragmentation cannot occur, and the material partially decomposes under the reaction conditions. Finally, by starting from the furanic β-ketosulfone **17g** and representative aldehydes **2a** and **2g**, the Michael adduct was the major product and no sulfonyl-substituted oxepanol could be detected.

With the feasibility of the hetero-MARDi cascade having been established in the case of oxepanes and oxepines, we logically tried to extend the method to the synthesis of azepanes (or azepines) and thiepanes (or thiepines). Under the now well established optimised conditions of the cascade, the pyrrolidone **18a**[35] resulted almost exclusively in the formation of the diester **24** by retro-Dieckmann ring opening of the starting material (Table 8, entry 1). Actually, this result is not surprising considering that the MARDi cascade is performed under thermodynamic conditions, and the pyrrolidone **18a** is the kinetic product of the Dieckmann cyclisation of the diester **24** (the thermodynamic product is the isomeric pyrrolidone **18b**).[35] Indeed, the reaction between the pyrrolidone **18b** and acrolein provided a 1:1 mixture of the expected hydroxyazepanes **25a** (dr = 3.5:1) and the corresponding azepine **25b** (R = Me) in 36% yield (entry 2). Increasing the quantity of K_2CO_3 to 1 and 1.5 equivalents favoured the formation of the dehydrated product **25b** (R = Me) without significant alteration of the global yield (entries 3 and 4). However, in the latter case, the crude product was very clean and contained only the dehydrated product **25b** (R = Me), so the aqueous layer was acidified and extracted again to provide 51% of the acid **25b** (R = H). The structure of **25b** (R = H) was confirmed by conversion to its methylester by treatment with trimethylsilyldiazomethane.[26] Not surprisingly, the reaction of pyrrolidone **18b** with cyclopentene carboxaldehyde (**2n**) provided the hydroxyazepane **25c** and the azepine **25d** (dr = 1.6:1) with a yield and ratio hydroxyazepane/azepine similar to those obtained in the reaction with acrolein (compare entries 3 and 5). The bicyclo[5.3.0]decanol **25c** exhibits an all-*trans* relationship of the substituents on the seven-membered ring as proven by X-ray diffraction analysis.[16] As expected, the reaction of **18b** with methacrolein (**2g**) provided the carboxylic acid **25e**, albeit in very low yield (entry 6), the major product being the corresponding Michael–retro-Dieckmann aldehyde. Finally, in the sulfur series from the commercially available thiafuranone **19**, the MARDi cascade was also successful under the standard conditions. Thiepines **26a–c** were obtained with aldehydes **2a**,**b**,**n**, respectively, following dehydration of the intermediate hydroxythiepane (entries 7–9), and the carboxylic acids **26d** and **26f** could be isolated with aldehydes **2g** and **2i**, respectively (entries 10 and 11). However, for the reaction with methacrolein (entry 10), 17% of the corresponding dimethylester **26e** was also isolated as a 57:43 inseparable mixture of isomers (1,3-*cis* major). This gives a further argument for the proposed tandem intramolecular lactonization–elimination mechanism in the case of 2-substituted acroleins, leading to the dehydrated seven-membered ring carboxylic acids (Scheme 6b), as the water produced on dehydration of the dimethylester hydroxythiepane does not lead to the saponification of the non-conjugated ester group in the 1,3-*trans* dimethyl ester thiepine. In this case, the dehydration of the transient hydroxy thiepane, resulting from a poorly diastereoselective MARDi cascade, to give **26e** is in competition with the intramolecular lactonization–elimination mechanism proposed for the formation of **26d**.

When the MARDi cascade is performed with pyrrolidone **18b** or thiofuranone **19**, the presence of the heteroatom β to the hydroxyl group in the cycloheptanol clearly favours the dehydration. In almost every case, the best yield of hetero-MARDi product was obtained with thiofuranone **19**. This can be rationalised by the relative higher acidity of the proton α to the sulfur atom compared to nitrogen, which might accelerate the dehydration process, thus avoiding unwanted over reaction of the cycloheptanol.

Conclusion

We have demonstrated that the MARDi cascade (up to five steps in the domino process) allows regio- and stereocon-

Table 8. The MARDi cascade for the preparation azepanes, azepines and thiepines.[a]

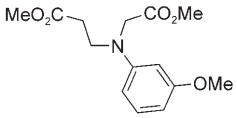
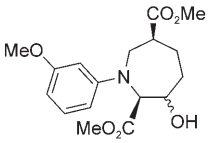
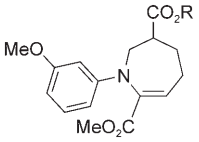
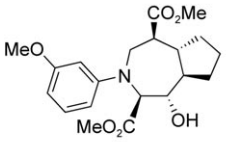
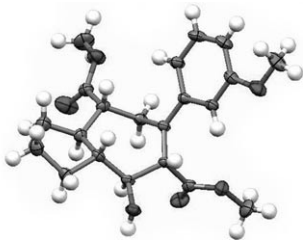
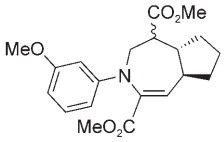
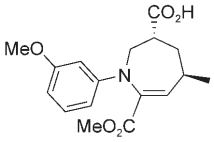
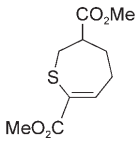
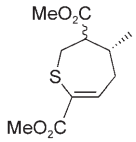
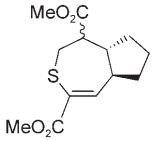
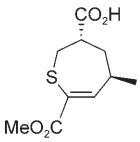
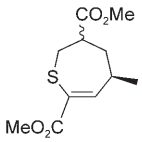
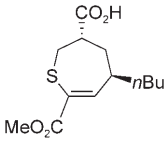
Entry	Substrate	Aldehyde	Product[b]	Yield [%][c]
1[d]	**18a**	**2a**,**b** and **2g**	 **24**	64–70
2[e]	**18b**	**2a**	 **25a**[f]  **25b**: R = H, Me	19 (**25a**), 17 (**25b**: R = Me)
3[g]	**18b**	**2a**	**25a** and **25b**	8 (**25a**), 25 (**25b**: R = Me)
4[h]	**18b**	**2a**	**25a** and **25b**	0 (**25a**) 31 (**25b**: R = Me) 51 (**25b**: R = H)
5[i]	**18b**	**2n**	 **25c** =   **25d**[j]	10 (**25c**) 22 (**25d**)
6[k]	**18b**	**2g**	 **25e**	7
7[e]	**19**	**2a**	 **26a**	55
8[i]	**19**	**2b**	 **26b**[l]	58

Table 8. (Continued)

Entry	Substrate	Aldehyde	Product[b]	Yield [%][c]
9[i]	**19**	**2n**	 **26c**[m]	28
10[k]	**19**	**2g**	 **26d**[n]  **26e**[m]	51 (**26d**) 17 (**26e**)
11[k]	**19**	**2i**	 **26f**[o]	42

[a] Unless stated otherwise, all reactions were performed in dry MeOH (0.04 M) with 1.5 equiv of aldehyde at room temperature for 20 h. [b] For **25a**, **25d**, **26b**, **26c** and **26e**, the major isomer is the thermodynamically favoured isomer (α-OH or β-CO_2Me). The relative configurations of compounds **25a**, **25c–e** and **26b–f** have been established by 2D NMR spectroscopic techniques and the structure of **25c** has been secured by X-ray diffraction analysis (see reference [16]). [c] Isolated. [d] K_2CO_3 or DBU (0.5 or 1 equiv). [e] K_2CO_3 (0.5 equiv). [f] dr = 3.5:1. [g] K_2CO_3 (1 equiv). [h] K_2CO_3 (1.5 equiv). [i] DBU (1 equiv). [j] dr = 1.6:1. [k] DBU (0.5 equiv). [l] dr = 5:1. [m] dr = 1.3:1. [n] dr = 17:1. [o] dr = 10:1.

trolled access to a variety of functionalised and substituted seven-membered rings. This new multicomponent reaction is a condensation and thus no byproducts are formed, except for water when dehydration is observed. The substitution array can be diastereoselectively modulated by appropriate choice of the reaction partners, and the reaction allows the control of up to five newly created stereocentres and a complete chiral induction in the case of an optically active ketone precursor in a single operation. The high level of diastereoselectivity observed has been attributed to total thermodynamic control of the reaction. The attractiveness of the present three-component domino approach to seven-membered rings resides in the diversity of carbo- and heterocyclic structures that can be accessed with total regiocontrol and high stereocontrol by starting from simple substrates, under user and environmentally friendly conditions, as now required in modern organic chemistry. Our work now focuses on the asymmetric version of the MARDi cascade and its applications to the total synthesis natural products.

Experimental Section

General: All reactions were performed in oven-dried glassware under an argon atmosphere. All reagents were obtained from commercial sources and used as supplied unless otherwise stated. MeOH was dried by refluxing with magnesium and then distilled under an argon atmosphere. K_2CO_3 and Cs_2CO_3 were dried by prolonged storage at 140 °C in an oven. Pyridine and triethylamine were dried over solid KOH and distilled under an argon atmosphere. HMPA was dried by refluxing with CaH_2 and distilled under an argon atmosphere. Petroleum ether refers to the fraction of petroleum ether that was distilled between 40 and 65 °C. Aldehydes **2** and the Dieckmann esters **1a**,**b** were distilled prior use. The reactions were monitored by TLC, which was performed on Merck 60F254 plates and visualised with an ethanolic solution of *p*-anisaldehyde and sulfuric acid or an ethanolic solution of molybdophosphoric acid. Flash chromatography was performed with Merck 230–400 mesh silica gel. NMR spectroscopic data were recorded on a Brüker AC 200, Avance 300 or Avance 400 spectrometer in $CDCl_3$ or $(CD_3)_2CO$, and chemical shifts (δ) are given in ppm relative to the residual non-deutered signal for ^{1}H NMR spectra ($CHCl_3$: $\delta = 7.26$ ppm) and relative to the deuterated solvent signal for ^{13}C NMR spectra ($CDCl_3$: 77.0 ppm, $(CD_3)_2CO$: 29.8 ppm); coupling constants (J) are in Hertz, and the classical abbreviations are used to describe the signal multiplicity; peak assignment and relative configurations have been established from standard COSY, NOESY, HMQC and HMBC experiments. Mass spectra were recorded on an API III Plus Sciex spectrometer equipped with an electrospray ionisation source and a triple quadripole detector or on a Brüker Esquire 6000 spectrometer equipped with an electrospray ionisation source and an ion-trap detector. Optical rotations were recorded on a Perkin–Elmer 241 polarimeter at 25 °C, path length = 10 cm, by using a sodium lamp as the light source. Melting points are uncorrected and were measured with a Büchi B-540 apparatus. Elemental analyses were performed on a Thermo Finnigan EA 1112 analyser.

General procedure for compounds of type 4: The procedure for (+)-**4h** is representative for all compounds of type **4**.

Compound 4h: An oven dried, two-necked, round-bottomed flask under an argon atmosphere and equipped with a magnetic Teflon-coated stirring bar was charged at room temperature with β-ketoester (+)-**1c** (498 mg, 3.19 mmol) and MeOH (10 mL) in that order. At 0 °C, DBU (480 μL, 3.22 mmol) was added and the mixture was stirred for 10 min, then crotonaldehyde (**2b**) (400 μL, 4.83 mmol) was added. The reaction mixture was slowly warmed to room temperature and stirred at that temperature for 21 h. Most of the methanol was then removed under reduced pressure and water (20 mL) was added; the resulting aqueous medium

was extracted three times with diethyl ether and the combined organic layers were washed with brine, dried with anhydrous sodium sulfate, filtrated and then concentrated to give the crude product. The crude product was purified by flash chromatography on silica gel with diethyl ether in petroleum ether as the eluent to give 357 mg (43%) of **4h** as slightly yellow oil. $R_f = 0.37$ (Et_2O/petroleum ether 9:1); $[\alpha]_D = +28.3$ ($c = 1.15$ g per 100 mL in CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 3.92$ (ddd, ^3J(H,H) = 14.0, 10.0, 3.8 Hz, 1H), 3.69 (s, 3H), 3.64 (s, 3H), 2.33 (ddd, ^3J(H,H) = 12.0, 10.0, 6.4 Hz, 1H), 2.25 (dd, ^3J(H,H) = 10.0, 6.4 Hz, 1H), 1.95–2.12 (m, 2H), 1.62–1.75 (m, 3H), 1.46 (dd, ^3J(H,H) = 14.5, 3.0 Hz, 1H), 0.95 (d, ^3J(H,H) = 7.0 Hz, 3H), 0.93 ppm (d, ^3J(H,H) = 8.0 Hz, 3H), the hydrogen atom of the hydroxyl group was not detected; ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 176.2$ (C), 175.8 (C), 73.5 (CH), 53.2 (CH), 51.7 (CH_3), 51.5 (CH_3), 43.2 (CH), 33.7 (CH_2), 27.5 (CH), 25.0 (CH), 24.0 (CH_2), 22.6 (CH_3), 22.6 ppm (CH_3); MS (ESI+): m/z (%): 281 (100) $[M+Na]^+$; elemental analysis calcd (%) for $C_{13}H_{22}O_5$: C 60.45, H 8.58; found: C 60.34, H 8.49.

The characterization data for the cycloheptanols **4a**, **5a**, **4c** and **4e–g** have been reported previously (see reference [11a]).

Cycloheptanols 4b and 5b (1.5:1 mixture of isomers): ^{13}C NMR (50 MHz, $CDCl_3$): $\delta = 175.5$ (C), 175.4 (C), 175.0 (C), 174.9 (C), 73.1 (CH), 72.1 (CH), 60.0 (CH_2), 59.9 (CH_2), 59.8 (CH_2), 59.8 (CH_2), 53.7 (CH), 52.9 (CH), 43.9 (CH), 42.1 (CH), 33.4 (CH_2), 32.3 (CH_2), 28.8 (CH_2), 27.1 (CH_2), 25.2 (CH_2), 24.6 (CH_2), 23.8 (CH_2), 23.6 (CH_2), 13.6 (CH_3), 13.6 ppm (CH_3); MS (ESI+): m/z (%): 281 (100) $[M+Na]^+$; elemental analysis calcd (%) for $C_{13}H_{22}O_5$: C 60.45, H 8.58; found: C 60.81, H 8.89.

Cycloheptanol 4d: $R_f = 0.36$ (Et_2O/petroleum ether 9:1); ^{1}H NMR (200 MHz, $CDCl_3$): $\delta = 3.95$ (dt, ^3J(H,H) = 10.5, 2.4 Hz, 1H), 3.70 (s, 3H), 3.65 (s, 3H), 2.65 (d, ^3J(H,H) = 4.0 Hz, 1H), 2.22–2.40 (m, 2H), 1.68–2.08 (m, 6H), 1.05–1.65 (m, 4H), 0.82 ppm (t, ^3J(H,H) = 6.0 Hz, 3H), the hydrogen atom of the hydroxyl group was not detected; ^{13}C NMR (50 MHz, $CDCl_3$): $\delta = 176.3$ (C), 175.5 (C), 73.2 (CH), 54.1 (CH), 51.4 (CH_3), 51.2 (CH_3), 49.0 (CH), 35.1 (CH), 38.3 (CH_2), 38.2 (CH_2), 27.6 (CH_2), 23.1 (CH_2), 19.3 (CH_2), 13.8 ppm (CH_3); MS (ESI+): m/z (%): 295 (100) $[M+Na]^+$, 273 $[M+H]^+$; elemental analysis calcd (%) for $C_{14}H_{24}O_5$: C 61.74, H 8.88; found: C 61.92, H 9.02.

General procedure for compounds of type 8: The procedure for **8a** is representative for compounds of type **8**.

Compound 8a: An oven dried, two-necked, round-bottomed flask under an argon atmosphere and equipped with a magnetic Teflon-coated stirring bar was charged at room temperature with β-ketoester **1a** (561 mg, 3.95 mmol), MeOH (10 mL) and DBU (590 μL, 3.95 mmol) in that order. The resulting pale-yellow mixture was stirred at room temperature for 10 min, and then methacroleine (**2g**) (490 μL, 5.93 mmol) was added and the reaction mixture was stirred at the same temperature for 18 h. Most of the methanol was then removed under reduced pressure and water (25 mL) was added; the resulting basic aqueous medium was extracted twice with diethyl ether and then acidified to pH 1 with HCl (1 N) solution. The acidic aqueous layer was extracted three times with diethyl ether and the combined organic layers were dried with anhydrous sodium sulfate, filtrated and concentrated to give the crude clean product as a colourless oil suitable for analysis. ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 6.83$ (d, ^3J(H,H) = 4.5 Hz, 1H), 3.70 (s, 3H), 2.84 (qd, ^3J(H,H) = 16.0, 9.0 Hz, 1H), 2.70–2.80 (m, 1H), 2.61 (dd, ^3J(H,H) = 16.0, 9.0 Hz, 1H), 2.52 (dd, ^3J(H,H) = 16.0, 9.0 Hz, 1H), 2.03 (ddd, ^3J(H,H) = 14.0, 8.0, 2.7 Hz, 1H), 1.98 (ddd, ^3J(H,H) = 14.0, 5.0, 2.2 Hz, 1H), 1.66–1.83 (m, 2H), 1.20 ppm (d, ^3J(H,H) = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 181.8$ (C), 168.6 (C), 149.3 (CH), 133.3 (C), 51.9 (CH_3), 42.3 (C), 34.6 (CH_2), 30.5 (CH), 27.1 (CH_2), 24.3 (CH_2), 21.8 ppm (CH_3); MS (ESI-): m/z (%): 211 (100) $[M-H]^+$; elemental analysis calcd (%) for $C_{11}H_{16}O_4$: C 62.25, H 7.60; found: C 62.09, H 7.75.

The characterization data for the cycloheptenic acids **8b–i** have been reported previously (see reference [18]). These data are actually for the products with the *trans* relative configuration, and not *cis* as published at the time.

Cycloheptenic acid 8j: ^{1}H NMR (200 MHz, $CDCl_3$): $\delta = 6.82$ (d, ^3J(H,H) = 4.5 Hz, 1H), 4.15 (q, ^3J(H,H) = 7.1 Hz, 2H), 2.37–2.87 (m, 5H), 1.66–2.05 (m, 4H), 1.21 (t, ^3J(H,H) = 7.1 Hz, 3H), 1.12 ppm (t, ^3J(H,H) = 7.2 Hz, 3H); ^{13}C NMR (50 MHz, $CDCl_3$): $\delta = 181.0$ (C), 168.0 (C), 148.9 (CH), 133.4 (C), 60.6 (CH_2), 42.1 (CH), 34.5 (CH_2), 30.3 (CH), 27.0 (CH_2), 24.1 (CH_2), 21.7 (CH_3), 14.1 ppm (CH_3); MS (ESI-) m/z (%): 225 (100) $[M-H]^+$; elemental analysis calcd (%) for $C_{12}H_{18}O_4$: C 63.70, H 8.02; found: C 63.55, H 7.74.

Cycloheptandiol 9: A solution of osmium tetroxide in toluene (0.10 M, 4.3 mL, 0.430 mmol) was added to a solution of **8a** (84 mg, 0.396 mmol) in diethyl ether/pyridine (5:1, 6 mL) at 0 °C. The reaction mixture was stirred at 0 °C for 30 min and then 40% $NaHSO_3$ (4 mL) was added. The reaction mixture was vigorously stirred at room temperature for 13 h and then concentrated HCl (1 mL) was added. The organic layer was separated and the remaining aqueous layer was extracted four times with ethyl acetate. The combined organic layers were dried with anhydrous sodium sulfate, filtrated and then concentrated to give the crude product which was recrystallised from ethyl acetate/hexane by slow evaporation at room temperature to provide 81 mg (83%) of **9** as white needles suitable for X-ray diffraction analysis: $R_f = 0.46$ (AcOEt); m.p. 137 °C; ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 3.81$ (s, 3H), 3.49 (brs, 1H), 3.44 (d, ^3J(H,H) = 9.9 Hz, 1H), 2.67 (dddd, ^3J(H,H) = 10.5, 6.7, 6.7, 3.1 Hz, 1H), 2.20 (dddd, ^3J(H,H) = 14.3, 10.9, 10.8, 2.7 Hz, 1H), 1.70–2.05 (m, 6H), 1.59 (ddd, ^3J(H,H) = 15.6, 9.1, 6.8 Hz, 1H), 1.06 ppm (d, ^3J(H,H) = 6.9 Hz, 3H), CO_2H peak masked; ^{13}C NMR (75 MHz, $(CD_3)_2CO$): $\delta = 20.5$ (CH_3), 22.9 (CH_2), 32.7 (CH), 33.2 (CH_2), 35.1 (CH_2), 41.4 (CH), 52.6 (CH_3), 79.9 (C), 81.2 (CH), 177.3 (C), 177.5 ppm (C); MS (ESI-) m/z (%): 245 (100) $[M-H]^-$.

General procedure for compounds of type 15: The procedure for **15b** is representative for compounds of type **15**.

Compound 15b: An oven dried, two-necked, round-bottomed flask under an argon atmosphere and equipped with a magnetic Teflon-coated stirring bar was charged at 0 °C with β-ketosulfone **12a** (401 mg, 1.79 mmol), 1:1 MeOH/THF (30 mL) and K_2CO_3 (246 mg, 1.79 mmol) in that order. The resulting mixture was stirred at 0 °C for 5 min and then crotonaldehyde (**2b**) (220 μL, 2.66 mmol) was added. The reaction mixture was slowly warmed to room temperature, stirred at this temperature for 20 h (including ramp-up time), filtered through a pad of Celite and then concentrated. The solid obtained was partially dissolved in dichloromethane, filtrated over Celite and concentrated again to give 524 mg (90%) of the clean crude product. The major diastereomer was precipitated from diethyl ether and recrystallised from ethanol to give 295 mg (51%) of pure **15b** as white needles suitable for X-ray diffraction analysis. $R_f = 0.74$ (AcOEt); m.p. 144 °C; ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 7.84–7.89$ (m, 2H), 7.61–7.69 (m, 1H), 7.52–7.59 (m, 2H), 3.99 (brt, ^3J(H,H) = 9.6 Hz, 1H), 3.68 (s, 3H), 2.76 (ddd, ^3J(H,H) = 11.8, 5.5, 3.1 Hz, 1H), 2.49–2.66 (m, 2H), 2.37 (ddd, ^3J(H,H) = 12.2, 9.6, 3.5 Hz, 1H), 2.11–2.24 (m, 2H), 1.93 (ddd, ^3J(H,H) = 14.7, 10.5, 3.8 Hz, 1H), 1.77 (ddd, ^3J(H,H) = 15.0, 6.7, 1.8 Hz, 1H), 1.67 (dd, ^3J(H,H) = 12.9, 11.4 Hz, 1H), 1.38 (dd, ^3J(H,H) = 13.2, 11.6 Hz, 1H), 1.12 ppm (d, ^3J(H,H) = 7.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 175.1$ (C), 137.6 (C), 133.8 (CH), 129.2 (2CH), 128.9 (2CH), 70.7 (CH), 68.2 (CH), 54.4 (CH), 52.0 (CH_3), 39.5 (CH_2), 27.4 (CH), 26.5 (CH_2), 24.8 (CH_2), 22.8 ppm (CH_3); MS (ESI+): m/z (%): 344 (100) $[M+NH_4]^+$, 327 $[M+H]^+$; elemental analysis calcd (%) $C_{16}H_{22}O_5S$: C 58.87, H 6.79, S 9.82; found: C 58.47, H 6.66, S 9.62.

The characterization data for the cycloheptanols **15a**,**c–e** have been reported previously (see reference [21]).

The experimental protocol and the characterization data for the heterocyclic seven-membered rings **21a–e**, **25a–e**, **26a–d** and **26f** have been reported previously (see reference [30]). The structures of compounds **13**, **14**, **20**, **22** and **23** were determined by ^{13}C NMR and mass spectroscopy of the crude material and the products were not further characterised.

Thiepine *trans*-26e: This compound has been prepared by treatment of the corresponding carboxylic acid **26d** with $TMSCHN_2$ as described in reference [30]. $R_f = 0.56$ (AcOEt/petroleum ether 3:7); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 6.93$ (d, ^3J(H,H) = 4.9 Hz, 1H), 3.75 (s, 3H), 3.71 (s, 3H), 3.26 (dd, ^3J(H,H) = 14.1, 8.2 Hz, 1H), 3.01 (dddd, ^3J(H,H) = 8.2, 4.4, 4.1, 4.0 Hz, 1H), 2.87–2.98 (m, 1H), 2.87 (dd, ^3J(H,H) = 14.1, 4.1 Hz, 1H), 1.91–2.09 (m, 2H), 1.16 ppm (d, ^3J(H,H) = 7.2 Hz, 3H); ^{13}C NMR

(75 MHz, $CDCl_3$): δ 173.9 (C), 165.9 (C), 148.9 (CH), 130.2 (C), 52.6 (CH_3), 52.0 (CH_3), 43.2 (CH), 33.8 (CH_2), 33.1 (CH_2), 31.3 (CH), 22.2 ppm (CH_3); MS (ESI+): *m/z* (%): 362 (100) $[M+NH_4]^+$, 245 $[M+H]^+$; elemental analysis calcd (%) for $C_{11}H_{16}O_4S$: C 54.08, H 6.60, S 13.12; found: C 54.37, H 6.76, S 12.94.

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