

# From the MARDi Cascade to the Stereoselective Construction of Functionalized Bicyclo[5.4.0]undecene Skeletons Occurring in Natural Compounds

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Received August 26, 2003; Accepted September 23, 2003

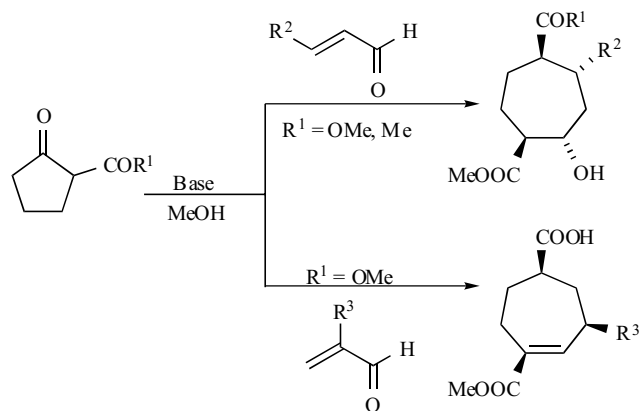
**Abstract:** The stereoselective construction of functionalized bicyclo[5.4.0]undecene systems, found in many natural sesquiterpenes such as in the widdrane, guadalupe, and recently isolated guanacastepene families, is achieved by selective chemical transformations of a functionalized cycloheptanol arising from the MARDi cascade.

**Keywords:** MARDi Cascade, Seven-membered Rings, Bicyclo[5.4.0]undecenes

Seven-membered carbocycles are often involved in the construction of elaborated bio-active natural compounds [1]. Specially, the bicyclo[5.4.0]undecane skeleton [2] is an important fused ring system found in relatively simple sesquiterpenes [3] and in more complicated di- and triterpenes [4] as well as in some highly functionalized alkaloids [5]. We have recently found the MARDi (Michael Addition Retro Dieckmann) cascade (Scheme 1), a new powerful anionic domino reaction for the stereoselective two-carbon ring expansion of cyclopentanones leading to the synthesis of highly functionalized and stereodefined seven-membered rings [6].

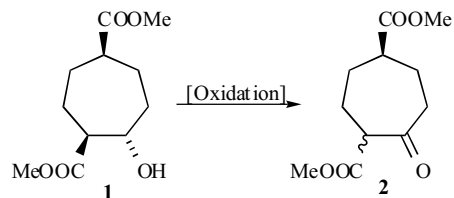
As part of this program, we wish to report here the stereoselective transformation of cycloheptanol **1**, very easily obtained by the MARDi cascade using Dieckmann ester and acrolein [6], into the basic bicyclo[5.4.0]undecene framework found in widdrane, guadalupe and recently isolated guanacastepene [7] sesquiterpenes.

Our approach is based on the reactivity of  $\beta$ -ketoester **2** used as nucleophile in the Michael addition to  $\alpha,\beta$ -unsaturated acyclic ketones **3**. To this end, we first studied the direct oxidation of **1** to **2**, which proved not to be trivial as shown by the results presented in Table 1. Among seven different reagents, only two gave a satisfactory transformation. Chromic oxidations[8] (entries 1-3) as well as attempted oxidations with *o*-iodoxybenzoic acid (IBX)[9] (entry 4) and copper nitrate[10] (entry 5) revealed totally unsuccessful. In contrast, treatment with tetra-*n*-propylammonium perruthenate (TPAP) [11] gave a 65% yield of **2** (entry 6) but proved to be less efficient on scaling-up the reaction. Finally, the best result was obtained with the Swern conditions using oxalyl chloride[12] which allowed the preparation of the required precursor in good yield even on gram-quantities (entry 7) [13].



Scheme 1. The MARDi cascade.

Table 1. Oxidation of **1** to  $\beta$ -Ketoester **2**.



Entry	Reagent	yield of <b>2</b> (%) <sup>a</sup>
1	PDC, CH <sub>2</sub> Cl <sub>2</sub>	-
2	PCC on Al <sub>2</sub> O <sub>3</sub>	-
3	Jones reagent	-
4	IBX, DMSO	-
5	Cu(NO <sub>3</sub> ) <sub>2</sub> , SiO <sub>2</sub>	-
6	TPAP, NMO, 4Å MS	65
7	(CO) <sub>2</sub> (Cl) <sub>2</sub> , DMSO	87

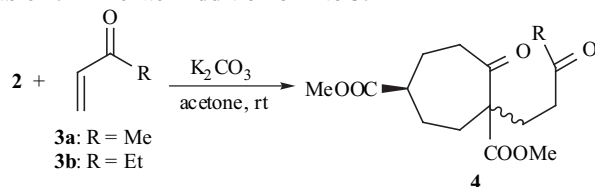
<sup>a</sup>Isolated (mixture of epimers and enol form).

With the required seven-membered ring ketoester **2** in hand we next studied the Michael addition to vinyl ketones

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**3** (Table 2). The best results were obtained in acetone at room temperature by using  $K_2CO_3$  as base. The corresponding 1,5-dicarbonyl intermediates **4a,b** were isolated after filtration through a short pad of celite with 97% and 96% yield, respectively. The condensation proceeded with modest facial diastereoselectivity in favor of the isomer having the two carbomethoxy groups in a *cis* relationship.

**Table 2. Michael Addition of 2 to 3.**

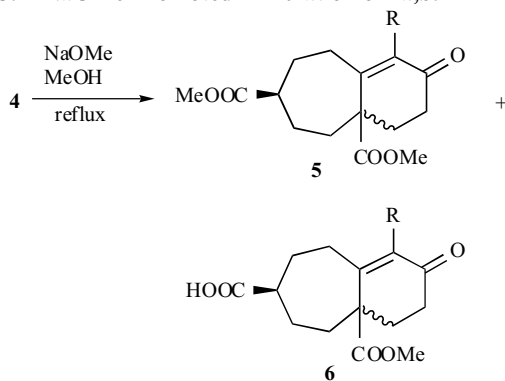


Vinyl ketone	Time (h)	4 (ratio) <sup>a</sup>	Yield (%) <sup>b</sup>
3a, R = Me	3	4a (4/1)	97
3b, R = Et	4	4b (3/1)	96

<sup>a</sup>Determined by  $^1H$  NMR. <sup>b</sup>Isolated.

Finally, the construction of the bicyclo[5.4.0]undecene skeletons **5** was easily achieved by reaction of **4a,b** with NaOMe in refluxing methanol (Table 3). Interestingly, while the yields of the annelation were good, we always observed the formation of a mixture of the bicyclic diesters **5a,b** and the corresponding monoacids **6a,b** arising from the selective saponification of one of the two carbomethoxy groups (Table 3).

**Table 3. NaOMe Promoted Annelation of 4a,b.**



Substrate	Time (h)	Ratio 5:6 <sup>a</sup>	Yield (%) <sup>b</sup>
4a, R = Me	4	1:2.3 (R = H)	82
4b, R = Et	5	2.8:1 (R = Me)	96

<sup>a</sup>Determined by  $^1H$  NMR. <sup>b</sup>Isolated.

These preliminary results show that the cycloheptanols obtained by the MARDi cascade coupled with standard chemical transformations can be interesting starting materials

for the selective construction of more elaborated skeletons found in natural sesquiterpenes. Further synthetic exploitations of this valuable transformation are under active investigation.

## REFERENCES

- [1] For general reviews, see: Heathcock, C. H.; Gram, S. L.; Pirrung, M. C.; Plavac, F.; White, C. T. In *The Total Synthesis of Natural Products*, ApSimon, J. Ed.; Wiley: New York, **1983**; Vol. 5, pp. 333-384; Rigby, J. H. In *Studies in Natural Products Chemistry (Part A)*, A. Rhaman, Ed.; Elsevier: New York, **1988**; Vol. 1, pp. 545-576; Vandewalle, M.; De Clercq, P. *Tetrahedron*, **1985**, *41*, 1767-1831. Yet, L. *Tetrahedron* **1999**, *55*, 9349-9403. Yet, L. *Chem. Rev.* **2000**, *100*, 2963-3007. Kantorowski, E. J.; Kurth, M. J. *Tetrahedron* **2000**, *56*, 4317-4353. Harmata, M.; Rashatasakhon, P. *Tetrahedron* **2003**, *59*, 2371-2395.
- [2] Lautens, M.; Kumanovic, S. *J. Am. Chem. Soc.*, **1995**, *117*, 1954-1964.
- [3] Shastri, M. H.; Dev, S. *Tetrahedron Lett.*, **1992**, *48*, 4905-4918; Gonzalez, A. G.; Darias, J.; Martin, J. D.; Melian, M. A. *Tetrahedron Letters*, **1978**, 481-482; Liu, H.-J.; Browne, E. N. C. *Can. J. Chem.*, **1981**, *59*, 601-608; Ho, T.-L.; Yang, P.-F. *Tetrahedron*, **1995**, *51*, 181-192.
- [4] For selected examples of diterpenes, see: Wender, P. A.; McDonald, F. E. *J. Am. Chem. Soc.*, **1990**, *112*, 4956-4958; Metz, P.; Bertels, S.; Fröhlich, R. *J. Am. Chem. Soc.*, **1993**, *115*, 12595-12596; Williams, D. R.; Coleman, P. J.; Henry, S. H. *J. Am. Chem. Soc.*, **1993**, *115*, 11654-11655; Kan, T.; Hosokawa, S.; Nara, S.; Oikawa, M.; Ito, S.; Matsuda, F.; Shirahama, H. *J. Org. Chem.*, **1994**, *59*, 5532-5534; McMills, M. C.; Zhuang, L.; Wright, D. L.; Watt, W. *Tetrahedron Lett.*, **1994**, *35*, 8311-8314; Metha, G.; Umarey, J. D.; Srinivas, K. *Tetrahedron Lett.*, **2003**, *44*, 4233-4237. For selected examples of triterpenes, see: Majetich, G.; Zhang, Y. *J. Am. Chem. Soc.*, **1994**, *116*, 4979-4980.
- [5] Banwell, M. G.; Lambert, J. N.; Mackay, M. F.; Greenwood, R. J. *J. Chem. Soc., Chem. Commun.*, **1992**, 974-975; Joshi, B. S.; Pelletier, S. W.; Zhang, X.; Snyder, J. K. *Tetrahedron*, **1991**, *47*, 4299-4316; Srivastava, S. K.; Joshi, B. S.; Newton, M. G.; Lee, D.; Pelletier, S. W. *Tetrahedron Lett.*, **1995**, *36*, 519-522.
- [6] Filippini, M. H.; Rodriguez, J.; Santelli, M. *J. Chem. Soc., Chem. Commun.* **1993**, 1647-1648. Filippini, M. H.; Rodriguez, J.; Faure, R. *J. Org. Chem.* **1995**, *60*, 6872-6882. Filippini, M. H.; Rodriguez, J. *J. Org. Chem.*, **1997**, *62*, 3034-3035.
- [7] Brady, S.F.; Singh, M.P.; Janso, J.E.; Clardy, J. *J. Am. Chem. Soc.*, **2000**, *122*, 2116-2117; Brady, S.F.; Bondi, S.M.; Clardy, J. *J. Am. Chem. Soc.*, **2001**, *123*, 9900-9901.
- [8] Corey, E. J.; Schmidt, G. *Tetrahedron Lett.*, **1979**, 399-402; Piancatelli, G.; Scettri, A.; D'Auria, M. *Synthesis*, **1982**, 245-258.
- [9] Frigerio, M.; Santagostino, M.; Sputore, S.; Palmisano, G. *J. Org. Chem.*, **1995**, *60*, 7272-7276.
- [10] Nishiguchi, T.; Asano, F. *J. Org. Chem.*, **1989**, *54*, 1531-1535.
- [11] Griffith, W. P.; Ley, S. V.; Whitcombe, G. P.; White, A. D. *J. Chem. Soc., Chem. Commun.*, **1987**, 1625-1627.
- [12] Mancuso, A. J.; Huang, S.-L.; Swern, D. *J. Org. Chem.*, **1978**, *43*, 2480-2482.
- [13] Compound **2** prepared by the standard procedure reported in reference 12 has the following analytical data: colorless oil,  $R_f$  = 0.48 (Ethyl ether:pentane, 9:1); IR (neat) 2950, 2860, 1730, 1645, 1610, 1440, 1210  $cm^{-1}$ ;  $^1H$  NMR ( $CDCl_3$ , 200 MHz)  $\delta$  3.81 (3H, s), 3.65 (3H, s), 2.84-2.42 (2H, m), 2.21-1.51 (8H, m);  $^{13}C$  NMR ( $CDCl_3$ , 50.32 MHz)  $\delta$  200.6, 178.0, 174.1, 51.5, 51.3, 46.8, 43.0, 37.6, 32.5, 26.5, 25.9; Anal. Calcd. For  $C_{11}H_{16}O_5$ : C, 57.89; H, 7.07. Found: C, 58.09; H, 6.83.