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Stereoselective Synthesis of Bicyclo[4.2.1]nonane Skeletons by Ring-Closing Metathesis: A New Versatile Methodology for the Efficient Assembly of Functionalized Cyclooctanoids

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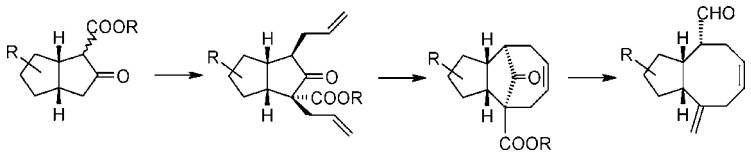
ABSTRACT



A new versatile methodology, resulting in a formal three-carbon ring expansion of cyclopentanones, for the efficient assembly of functionalized cyclooctanoids is described. The approach is based on the chemo-, regio-, and stereoselective α,γ-difunctionalization of β-ketoesters followed by ring-closing metathesis to form functionalized bicyclo[4.2.1]nonanes, precursors of the corresponding cyclooctanes, by selective ring cleavage of the one-carbon-atom bridge.

The occurrence of the cyclooctanoid system in a large number of biologically important natural and non-natural products has stimulated the development of many original approaches[1] and still constitutes a challenging synthetic target[2] as a result of the usually highly demanding direct cyclization to an eight-membered ring, which can hardly be constructed by conventional methods.[3] Among many clever methodologies developed, the temporary-bridge approach involving selective formation and subsequent fragmentation of bridged intermediates is particularly attractive because it takes advantage of the strain release during the formation of the eight-membered ring.[4] In this context, the functionalized bicyclo[4.2.1]nonane nucleus, which constitutes the key structural core of some bioactive natural products, can also serve as a potential precursor of eight-membered rings, providing selective cleavage of the one-carbon-atom bridge.[5] This interesting behavior, first observed by Carruthers[6] in

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(1) For reviews, see: Petasis, N. A.; Patane, M. A. *Tetrahedron* **1992**, *48*, 5757−5821. Mehta, G.; Singh, V. *Chem. Rev.* **1999**, *99*, 881−930.

(2) For selected recent approaches, see: Murakami, M.; Itami, K.; Ito, Y. *Synlett* **1999**, 951−953. Lee, Y.-g.; McGee, K. F., Jr.; Chen, J.; Rucando, D.; Sieburth, S. M. *J. Org. Chem.* **2000**, *65*, 6676−6681. Harmata, M.; Rashatasakhon, P. *Org. Lett.* **2000**, *2*, 2913−2915. Oh, H.-S.; Lee, H. I.; Cha, J. K. *Org. Lett.* **2002**, *4*, 3707−3709. Barluenga, J.; Diéguez, A.; Rodríguez, F.; Flórez, J.; Fananas, F. J. *J. Am. Chem. Soc.* **2002**, *124*, 9056−9057. Banerjee, S.; Ghosh, S. *J. Org. Chem.* **2003**, *68*, 3981−3989.

(3) Illuminati, G.; Mandolini, L. *Acc. Chem. Res.* **1981**, *14*, 95−102.

(4) For selected recent examples in the bridged [3.3.1] and [3.3.2] series, see: (a) Simon, C.; Peyronel, J.-F.; Clerc, F.; Rodriguez, J. *Eur. J. Org. Chem.* **2002**, 3359−3364. (b) Diez, D.; Parra, M.; San Feliciano, S. G.; Marcos, I. S.; Garrido, N. M.; Basabe, P.; Jimenez, A.; Broughton, H. B.; Urones, J. G. *Synth. Commun.* **2002**, *32*, 1829−1839. (c) Takeda, K.; Sawada, Y.; Sumi, K. *Org. Lett.* **2002**, *4*, 1031−1033.

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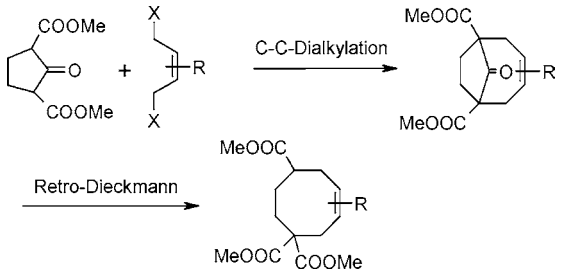
1973, found no further development because of the lack of general access to functionalized [4.2.1] bicyclic skeletons.[7] We have previously used this potentiality to describe a new temporary-bridge approach for the facile one-pot preparation of functionalized cyclooctenes using the selective formation and retro-Dieckmann fragmentation of bridged bicyclo[4.2.1]-nonan-9-ones[8] (Scheme 1).

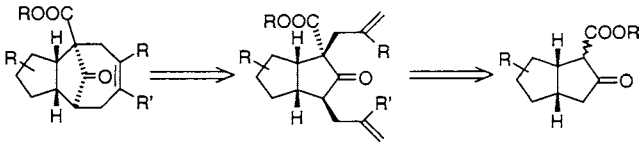
Scheme 1. Domino C−C-Cycloalkylation/Retro-Dieckmann Reaction



Following this work and very recently, Zhang[7d] and collaborators reported one example of an interesting intramolecular diazo ketone insertion followed by Grob-type fragmentation into the corresponding eight-membered ring. Contemporaneously, Mascareñas's group[9] disclosed a rapid and versatile approach based on ring-closing metathesis and subsequent $Pb(OAc)_4$-promoted ring cleavage of hydroxy bridgehead bicyclo[4.2.1]nonan-9-ones. These recent results combined with our continuing efforts in the development of the chemistry of functionalized bridged intermediates[10] prompted us to disclose our new contribution to the field.

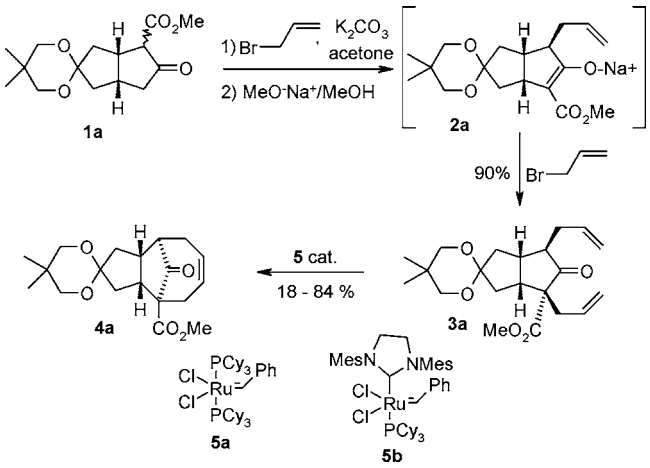
We have now planned to stereoselectively construct the key bicyclo[4.2.1]nonan-9-one core by ring-closing metathesis (RCM) of a properly functionalized intermediate with the required α,α′-*cis* stereochemistry obtained from readily accessible bicyclic ketoesters (Scheme 2).

Scheme 2. Retrosynthetic Analysis



Our approach takes advantage of the specific structure of the starting functionalized bicyclo[3.3.0]octane, which imposes a total diastereofacial control, combined with a new powerful domino anionic ring cleavage/ring formation/alkylation sequence resulting in a formal 1,3-ester shift.[11] This allowed a total control of the chemo-, regio-, and stereoselectivity of the *cis*-α,γ-difunctionalization required for the cyclization into bridged bicyclo[4.2.1]nonane intermediates. To test the validity of the new methodology, we first studied the stereoselective *cis*-α,γ-diallylation of β-ketoester **1a**[12] (Scheme 3). Reaction of **1a** with allyl bromide

Scheme 3. Overall Sequence for Preparation of Bicyclo[4.2.1]nonanes



in acetone in the presence of K_2CO_3[13] followed by the domino 1,3-ester shift-allylation protocol, accomplished using MeO^-Na^+/MeOH, gave the stabilized enolate intermediate **2a**, which upon reaction with allyl bromide in a one-pot process furnished the desired *cis*-α,γ-diallylated cyclopentanone **3a** in 90% overall yield as only one diastereomer.[14] Although ring-closing metathesis has emerged as one of the most powerful methods in modern organic synthesis, only a few reports have dealt with the stereoselective construction of related bridged carbobicyclic systems.[15] In the case of **3a**,

(5) For a review on the synthesis and reactivity of bicyclo[4.2.1]nonanes, see: Casanova, J.; Koukoua, G.; Waegell, B. *Bull. Soc. Chim. Fr.* **1990**, 528−552.

(6) Carruthers, W.; Qureshi, M. I. *J. Chem. Soc., Perkin Trans. 1* **1973**, 51−52.

(7) For selected recent approaches, see: (a) Verma, S. K.; Nguyen, Q. H.; MacDougall, J. M.; Fleischer, E. B.; Moore, H. W. *J. Org. Chem.* **2000**, *65*, 3379−3386. (b) Beckwith, R. E. J.; Blake, A. J.; Simpkins, N. S.; Wilson, C.; Gravestock, M. B. *Chem. Commun.* **2000**, 1097−1098. (c) Srikrishna, A.; Ramachary, D. B. *Tetrahedron Lett.* **2000**, *41*, 2231−2233. (d) Chen, L.; Zhang, X.; Schultz, A. *Tetrahedron Lett.* **2002**, *43*, 4711−4715. (e) Wang, Y.; Schill, B. D.; Arif, A. M.; West, F. G. *Org. Lett.* **2003**, *5*, 2747−2750. (f) Lavoisier-Gallo, T.; Charonnet, E.; Rodriguez, J. *Synthesis* **1997**, 1258−1260.

(8) (a) Lavoisier-Gallo, T.; Charonnet, E.; Rodriguez, J. *J. Org. Chem.* **1998**, *63*, 900−902. (b) Lavoisier-Gallo, T.; Charonnet, E.; Pons, J.-M.; Rajzman, M.; Faure, R.; Rodriguez, J. *Chem. Eur. J.* **2001**, *7*, 1056−1068.

(9) Rodríguez, J. R.; Castedo, L.; Mascareñas, J. L. *Chem. Eur. J.* **2002**, *8*, 2923−2930.

(10) Contributions from this laboratory, see: (a) Rodriguez, J. *Synlett* **1999**, 505−518. (b) Filippini, M.-H.; Rodriguez, J. *Chem. Rev.* **1999**, *99*, 27−76. See also refs 4a and 8.

(11) This sequence is based on the pioneering work from Isida's group on retro-Dieckmann-Dieckmann condensation; see: Sisido, K.; Utimoto, K.; Isida, T. *J. Org. Chem.* **1964**, *29*, 2781−2782.

(12) Piers, E.; Karunaratne, V. *Can. J. Chem.* **1989**, *67*, 160−164. Ruest, L.; Blouin, G.; Deslongchamps, P. *Synth. Commun.* **1976**, *6*, 169−174.

(13) Barco, A.; Benetti, S.; Pollini, G. P. *Synthesis* **1973**, 316.

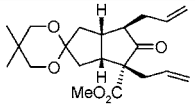
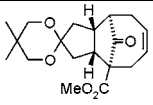
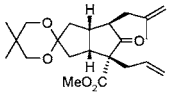
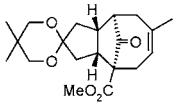
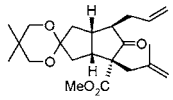
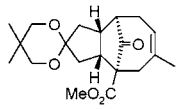
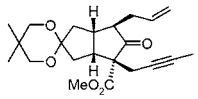
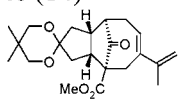
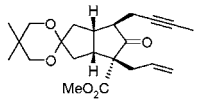
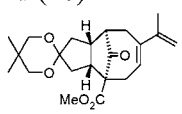
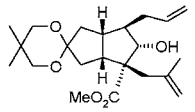
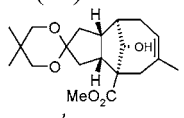
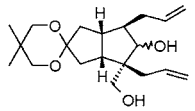
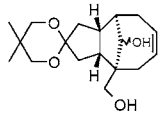
(14) The *cis*-α,γ-stereochemistry was deduced from NMR analyses including two-dimensonial experiments and confirmed by RCM.

(15) For the first report on the construction of related bridged systems using RCM, see: Morehead, A., Jr.; Grubbs, R. *Chem. Commun.* **1998**, 275−276. For other bridged systems, see: Kigoshi, H.; Suzuki, Y.; Aoki, K.; Uemura, D. *Tetrahedron Lett.* **2000**, *41*, 3927−3930. Tang, H.; Yusuff, N.; Wood, J. L. *Org. Lett.* **2001**, *3*, 1563−1566. Mehta, G.; Kumaran, R. S. *Chem. Commun.* **2002**, 1456−1457.

utilization of standard metathesis conditions with 5−10 mol % of catalyst **5a** in refluxing CH_2Cl_2 for up to 36 h resulted in almost no conversion of the starting material. Changing the solvent for toluene and using 20 mol % of **5a** allowed the isolation of the expected bridged bicyclic ketone **4a** in only 18% yield. Alternatively, addition of $Ti(OiPr)_4$ in order to prevent deactivation of the catalyst[16] allowed a 50% yield but using 10 mol % of **5a** in refluxing CH_2Cl_2 for 48 h. Finally, a reproducible yield in the range from 77% to 84% was achieved when only 2 mol % of the well-known, more active catalyst **5b**[17] was used in refluxing CH_2Cl_2 for only 3 h (Scheme 3).

With this encouraging result in hand, the overall transformation was successfully extrapolated to various substrates and proved to be quite general and versatile, as shown in Table 1. One of the main advantages of this new stereoselective approach is the flexibility of the introduction of the unsaturated substituent, which can be selected before or after the 1,3-ester shift. For example, allyl methallyl **3b**,**c** (entries 2 and 3) analogues were easily obtained and similarly transformed into the corresponding bicyclo[4.2.1]nonanones **4b**,**c** in good yields. Moreover, allyl propargyl derivatives **3d**,**e** (entries 4 and 5) are also easily accessible, selectively allowing the facile construction of bicyclo[4.2.1]nonanones **4d**,**e** having a valuable exocyclic 1,3-diene system. Finally, both hydroxyl derivatives **6** and **7**, arising from reduction with either $NaBH_4$ or $AlLiH_4$ were successfully cyclized, without protection, into the corresponding bicyclo[4.2.1]-nonanols **8** and **9** in 98% and 92% yield, respectively (entries 6 and 7). These two very efficient transformations stressed the beneficial effect of a free hydroxyl group on the rate of RCM.[18]

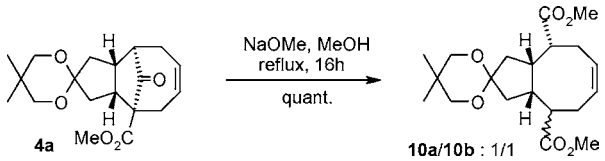
Table 1. Preparation of Bicyclo[4.2.1]nonanes **4**, **8**, and **9**[a]

entry	substrate	product (t, h)	yield (%)
1	 **3a**	 **4a** (3)	84
2	 **3b**	 **4b** (16)	70
3	 **3c**	 **4c** (14)	68
4	 **3d**	 **4d** (20)[c]	80
5	 **3e**	 **4e** (20)[c]	76
6	 **6**	 **8** (3)[d]	98
7	 **7**[e]	 **9** (2)[e,d]	92

[a] Unless otherwise noted all reactions were performed in refluxing CH_2Cl_2 at 6×10^{-3} mol/L using 2 mol % of **5b**. [b] Isolated by flash chromatography on SiO_2. [c] 6 mol % of **5b**. [d] Only 1 mol % of **5b** was used. [e] 4/1 mixture of diastereomers.

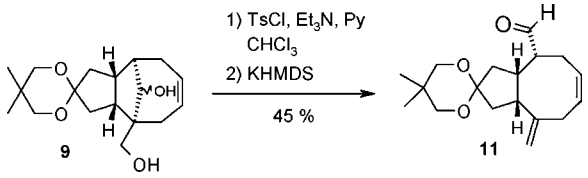
With these results, combined with our experience in the fragmentation of bridged bicyclic intermediates,[10] we first looked at the direct retro-Dieckmann cleavage of bridged ketone **4a** to liberate the corresponding fused eight-membered ring **10**.[19] Although we rapidly found optimum experimental conditions to cleave compound **4a** in quantitative yield (MeO^-Na^+, MeOH, reflux, 16 h), the reaction always led to a 1/1 mixture of isomers **10a** and **10b** (Scheme 4).

Scheme 4. Retro-Dieckmann Fragmentation of **4a**



Alternatively, bridged bicyclo[4.2.1]nonanols **9** were successfully transformed to the corresponding monotosylates precursor for a stereoselective Grob-type fragmentation upon reaction with KHMDS in THF. The expected bicyclo[6.3.0]-undecene skeleton **11** was formed diastereoselectively in 45% isolated yield together with unreacted starting material (Scheme 5).

Scheme 5. Grob-Type Fragmentation of Tricyclic Diols **9**



In summary, we have developed a new versatile methodology for the efficient assembly of functionalized cyclooctanoids combining a stereoselective anionic domino α,γ-difunctionalization of β-ketoesters with ring-closing metath-

(16) Fürstner, A.; Langemann, K. *J. Am. Chem. Soc.* **1997**, *119*, 9130−9136.

(17) Love, J. A.; Sanford, M. S.; Day, M. W.; Grubbs, R. H. *J. Am. Chem. Soc.* **2003**, *125*, 10103−10109.

esis and resulting in a formal three-carbon ring expansion. Work aimed at the development of this approach toward total synthesis of bidged-bicyclic rings and cyclooctanoid natural compounds is underway.

Acknowledgment. A.M. thanks the Ministère de l'Education Nationale de la Recherche et de la Technologie for a Ph.D. grant, and the authors gratefully acknowledge Comunidad Autónoma de Madrid for the financial support of a 3-month stay of S.M. in Marseille. NMR, mass spectra, and IR analyses were provided by the "Spectropole" facilities, Centre de St Jérôme.

Supporting Information Available: Experimental procedures; ^{1}H and ^{13}C NMR spectra and mass spectral analyses for compounds **3**, **4**, and **6**−**11**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(18) Although in some cases the presence of a free hydroxyl group has been shown to adversely affect the RCM, some results suggest this function could assist the process; see: Hoye, T. R.; Zhao, H. *Org. Lett.* **1999**, *1*, 1123−1125. Maishal, T. K.; Sinha-Mahapatra, D. K.; Paranjape, K.; Sarkar, A. *Tetrahedron Lett.* **2002**, *43*, 2263−2267. Caggiano, L.; Castoldi, D.; Beumer, R.; Bayon, P.; Telser, J.; Gennari, C. *Tetrahedron Lett.* **2003**, *44*, 7913−7919.

(19) While this manuscript was under evaluation, we were awarded of a related ring-closing metathesis/fragmentation methodology for the construction of medium-ring cycloalkenes: Ivkovic, A.; Matovic, R.; Saicic, R. N. *Org. Lett*. **2004**, *6*, 1221−1224.