ORGANIC
LETTERS

2000
Vol. 2, No. 20
3209−3212

An Expeditious Route to Eight- and Nine-Membered Carbocycles Based on a RCM-Ring Fragmentation Strategy[†]

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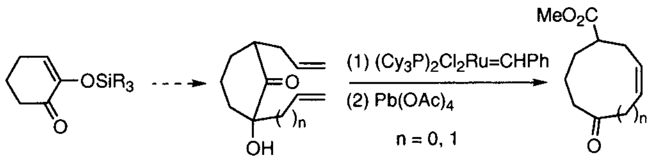
Received July 31, 2000

ABSTRACT



The presence of a temporary one-atom internal tether in 1,9-deca- and 1,10-undecadienes allows their efficient ring-closing metathesis (RCM). Cleavage of the bridging tether of the resulting bicycles provides eight- or nine-membered carbocycles, medium-sized rings that are difficult to assemble using other currently available procedures.

The construction of medium-sized carbocycles, particularly eight- and nine-membered ones, remains a major current synthetic challenge owing to their being the main structural motif of a growing number of natural products[1] and the well-known difficulties associated with their assembly via direct cyclization routes.[2] Several reports have shown that ring-closing olefin metathesis (RCM) can be used to construct these medium-sized rings; however its success is restricted to substrates bearing some sort of conformational constraint which bias the intra- over the intermolecular process.[3,4] Previous attempts to cyclize conformationally flexible acyclic dienes to eight-membered carbocycles were unsuccessful.[5] We envisaged that the presence of a temporary one-atom

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[†] Dedicated to Prof. J. Barluenga on the occasion of his 60th birthday.

(1) For reviews, see: (a) Oishi, T.; Ohtsuka, Y. In *Studies in Natural Products Synthesis*; Atta-ur-Rahman, Ed.; Elsevier: Amsterdam, 1989; Vol. 3, p 73. (b) Petasis, N. A.; Patane, M. A. *Tetrahedron* **1992**, *48*, 5757. (c) Rousseau, G. *Tetrahedron* **1995**, *51*, 2777. (d) Molander, G. A. *Acc. Chem. Res.* **1998**, *31*, 603. (e) Mehta, G.; Singh, V. *Chem. Rev.* **1999**, *99*, 881 and references therein. For recent approaches to eight-membered rings, see: (f) Paquette, L. A.; Sun, L.-Q.; Watson, T. J. N.; Friedrich, D.; Freeman, B. T. *J. Org. Chem.* **1997**, *62*, 4908. (g) Li, C.-J.; Chen, D.-L, Lu, Y.-Q.; Haberman, J. X.; Mague, J. T. *Tetrahedron* **1998**, *54*, 2347. (h) Paquette, L. A.; Nakatani, S.; Zydowsky, T. M.; Edmonson, S. D.; Sun, L.-Q. Skerlj, R. *J. Org. Chem.* **1999**, *64*, 3244. (i) Randall, M. L.; Lo, P. C−K; Bonitatebus, P. J.; Snapper, M. L. *J. Am. Chem.* Soc. **1999**, *121*, 4534. (j) Imai, A. E.; Sato, Y.; Nishida, M.; Mori, M. *J. Am. Chem.* Soc. **1999**, *121*, 1217. For recent approaches to nine-membered rings, see: (k) Boivin, J.; Pothier, J.; Ramos, L.; Zard, S. Z. *Tetrahedron Lett.* **1999**, *40*, 9239. (l) Rigby, J. H.; Fales, K. R. *Tetrahedron Lett.* **2000**, *39*, 1525.

(2) (a) Illuminati, G.; Mandolini, L. *Acc. Chem. Res.* **1981**, *14*, 95. (b) Mandolini, L. *Adv. Phys. Org. Chem.* **1986**, *22*, 1. (c) Kreiter, C. G.; Lehr, K.; Leyendecker, M.; Sheldrik, W. S.; Exner, R. *Chem. Ber.* **1991**, *124*, 3. (d) Eliel, E. L.; Wilen, S. H. *Stereochemistry of Organic Compounds*; John Wiley and Sons: New York, 1994.

(3) These constraints have been achieved either by using a preexisting ring or by introducing appropriate substituents in the acyclic precursors: (a) Miller, S. J.; Kim, S. H.; Chen, R.; Grubbs, R. H. *J. Am. Chem.* Soc. **1995**, *117*, 2108. (b) Fürstner, A.; Langemann, K. *J. Org. Chem.* **1996**, *61*, 8746. (c) Linderman, R. J.; Siedlecki, J.; O'Neill, S. A.; Sun, H. *J. Am. Chem.* Soc. **1997**, *119*, 6919. (d) Marsella, M. J.; Maynard, H. D.; Grubbs, R. H. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 1101. (e) Paley, R. S.; Estroff, L. A.; Gauguet, J.-M.; Hunt, D. K.; Newlin, R. C. *Org. Lett.* **2000**, *2*, 365. (f) Paquette, L. A.; Tae, J.; Arrington, M. P.; Sadoun, A. H. *J. Am. Chem. Soc.* **2000**, *122*, 2742 and references therein. (g) Maier, M. E. *Angew. Chem., Int. Ed.* **2000**, *39*, 2073. (h) Méndez-Andino, J.; Paquette, L. A. *Org. Lett.* **2000**, *2*, 1263.

(4) For recent reviews on RCM, see: (a) Schuster, M.; Blechert, S. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 2037. (b) Grubbs, R. H.; Chang, S. *Tetrahedron* **1998**, *54*, 4413. (c) Armstrong, S. K. *J. Chem. Soc., Perkin Trans. 1* **1998**, 371. (d) *Alkene Metathesis in Organic Synthesis*; Fürstner, A., Ed.; Springer: Berlin, 1998. (e) Wright, D. L. *Curr. Org. Chem.* **1999**, *3*, 211. (f) Phillips, A. J.; Abell, A. D. *Aldrichimia Acta* **1999**, *32*, 75. (g) Roy, R.; Das, S. K. *Chem. Commun.* **2000**, 519.

(5) Kirkland, T. A.; Grubbs, R. H. *J. Org. Chem.* **1997**, *62*, 7310. See also ref 3a.

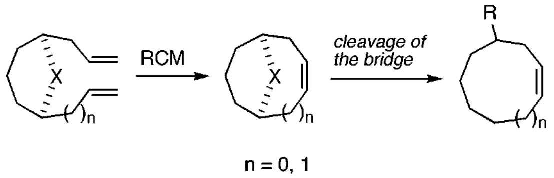
(6) The assembly of one-atom bridged bicycloalkenes by RCM of monocyclic precursors has been shown to be feasible: Morehead, A., Jr.; Grubbs, R. *Chem. Commun.* **1998**, 275.

(7) Mascareñas, J. L.; Rumbo, A.; Castedo, L. *J. Org. Chem.* **1997**, *62*, 8620.

10.1021/ol0063959 CCC: $19.00 © 2000 American Chemical Society
Published on Web 09/02/2000

internal tether in a diene precursor might decrease the activation barrier of the ring closure and hence allow the RCM to occur under relatively mild conditions (Scheme 1).[6]

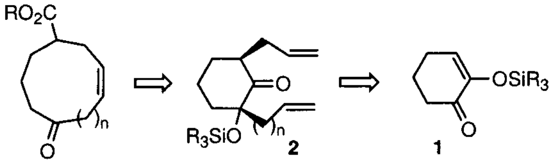
Scheme 1



Subsequent removal of the temporary bridge from the resulting bicyclic systems would lead to the otherwise difficult to assemble medium-sized rings. Herein we demonstrate the validity of this "temporary bridge" concept for the synthesis of eight- and nine-membered carbocycles.

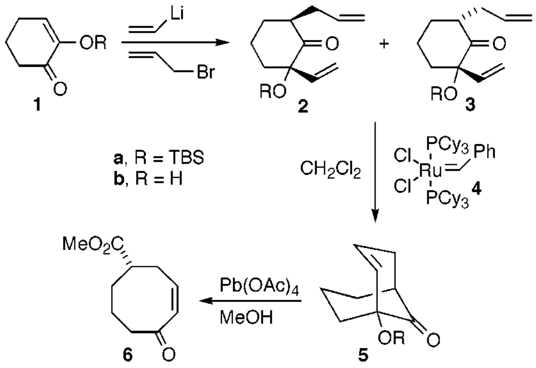
Our exact plan, outlined in Scheme 2, was designed on the basis of our recent results on the homologation of oxabicyclic [5 + 2] pyrone−alkene cycloadducts to *O*-bridged cyclonona- and cyclodecanoids.[7] A key element of the strategy is the use of an α-hydroxyketone as oxidatively cleavable internal tether. Although the requisite α,α′-dialkyl-α-silyloxycyclohexanones (**2**) could probably be readily assembled from an α-silyloxycyclohexenone (**1**) by means of an addition−silyl migration−enolate alkylation sequence, the stereochemical outcome of this process was difficult to predict.

Scheme 2



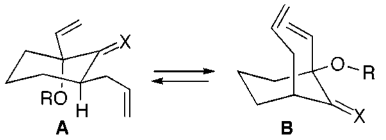
Treatment of enone **1a**[8] with vinyllithium and subsequent addition of allyl bromide (THF, −78 °C) led to the expected addition−alkylation product, as a 6:4 mixture of *cis* (**2a**) and *trans* (**3a**) isomers (83% combined yield, Scheme 3).[9] Although it was not possible to separate these isomers by simple chromatographic techniques, the viability of the cyclization was proved when the mixture was subjected to standard RCM conditions.[4] Hence, heating of this mixture in CH_2Cl_2 (approximately 0.05 M, 40 °C) for 12 h in the presence of 5% of ruthenium catalyst **4** produced the desired bicyclic derivative **5a** (15% yield from **1a**), which was easily separated from the uncyclized *trans* isomer **3a** by silica gel chromatography.

Scheme 3



We later found that removal of the silyl protecting group from the mixture of **2a** and **3a** (TBAF, THF) does allow chromatographic separation of the *cis* and *trans* isomers (**2b** and **3b**). Remarkably, whereas the RCM of **2a** (obtained by silylation of **2b**) required heat (40 °C, 18 h, 5 nM in CH_2Cl_2) and gave only a 65% yield of **5a**, alcohol **2b** smoothly cyclized at room temperature (20 °C, 9 h) to give the bicycle **5b** in 95% yield. This notable rate difference can be attributed to the equilibrium between **A** and **B** (see Table 1) being much more in favor of the RCM-reactive conformation **B** when R = H than when R = TBS, which is in consonance with the calculated steric energy difference between the two conformations. A great part of this difference in energy must arise from the existence of an intramolecular hydrogen bond which considerably stabilizes conformer **B** in the case of the α-hydroxycyclohexanone **2b** (R = H, X = O). Indeed, when R = H but the hydrogen bond is prevented by the carbonyl group being replaced by methylene (X = H, H), the conformer with the alkyl chains in a pseudoequatorial position (**A**) is still largely preferred.

Table 1. Difference in Steric Energy between the Two Chair Conformations **A** and **B**



entry	R	X	Δ*E*[a]
1	TBS	O	5.2
2	H	O	−0.3
3	TBS	H, H	4.5
4	H	H, H	2.9

[a] Approximate difference in steric energy between conformer **B** and conformer **A** (kcal/mol), calculated using the MM2 force field as implemented in Chem3D (Chem3Dpro 4.0, CSC, 1997).

With **5b** in hand we tested the feasibility of oxidative cleavage of the bridge. Gratifyingly, treatment of this

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(8) Prepared in quantitative yield from commercially available 1,2-cyclohexanedione using standard silylation conditions. See the Supporting Information for details.

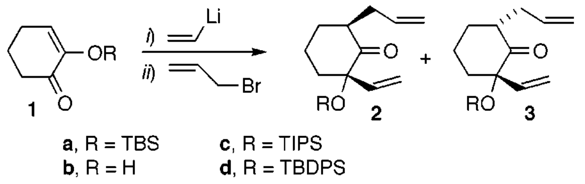
(9) The *cis*/*trans* ratio was deduced from the ^1H NMR spectrum of the mixture by integration of characteristic signals of each isomer, which could be assigned owing to the feasibility of obtaining the *trans* isomer in pure form after subjecting the mixture to the metathesis reaction (see discussion that follows in the main text).

compound with lead tetraacetate in MeOH induced instantaneous fragmentation of the bicycle to give the desired cyclooctenone **6** in a satisfactory 84% yield.[10]

The above results confirmed the validity of the cyclization−fragmentation tactic; however it was clearly desirable to increase its efficiency by either improving the stereoselectivity of the initial addition−alkylation reaction or by inducing *in situ* epimerization of the *trans* isomer **3** at the metathesis stage. The epimerization of **3a** or **3b** was easily promoted by treatment with catalytic amounts of KO^{t}Bu in *t*-BuOH/CH_2Cl_2 (or of DBU in CH_2Cl_2),[11] but these reagents were unfortunately found to inhibit the metathesis reaction, most probably by inactivating the catalyst. Use of an excess of the ruthenium catalyst with respect to the base did allow the RCM but suppressed the epimerization. On the other hand, all attempts to induce the epimerization under acidic conditions (AcOH or TfOH in aqueous CH_2Cl_2, or THF, or *p*-TsOH in toluene) were unsuccessful.

These failures, together with the finding that it is the undesired *trans* epimer that predominates under thermodynamic conditions (Table 2), led us to investigate the feasibility of improving the *cis*-stereoselectivity of the initial vinyl addition−enolate allylation step. We reasoned that increasing the bulk of the silyl migrating group might favor the formation of the desired *cis* isomer **2** by hindering the approach of the allyl bromide at the face bearing the silyloxy group. Indeed, use of TIPS (triisopropylsilyl) as protecting−migrating group slightly improved the *cis*/*trans* ratio, whereas the introduction of a TBDPS (*tert*-butyldiphenylsilyl) allowed us to obtain an acceptable proportion of the desired *cis* isomer (**2d**:**3d**, 2:1, Table 2).

Table 2. Kinetic and Thermodynamic Ratios of **2**:**3**

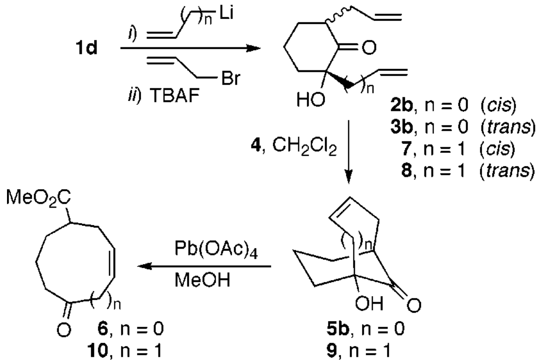


entry	enone[7]	yield, %[a]	**2**:**3**[8]	thermodynamic ratio of **2**:**3**[b]
1	**1a**	83	**2a**:**3a** (58:42)	**2a**:**3a** (30:70)
2	**1b**	<10	 (26:74)	**2b**:**3b**
3	**1c**	76	**2c**:**3c** (61:39)	**2c**:**3c** (44:56)
4	**1d**	78	**2d**:**3d** (67:33)	**2d**:**3d** (33:67)

[a] Combined isolated yield after chromatography. [b] Calculated after stirring the kinetic mixture with NaOMe in MeOH for 12 h.

On the basis of the above results, the whole alkylation−cyclization−fragmentation process was optimized to be carried out in three simple steps (Scheme 4): (1) addition of vinyllithium to **1d** and trapping of the resulting enolate with allyl bromide (THF, −78 °C), followed by *in situ* desilylation by treatment with TBAF (73% yield); (2) treatment of the resulting 2:1 mixture of **2b** and **3b** with the ruthenium catalyst **4** (7%, CH_2Cl_2, 20 °C, 9 h; 64% yield, 95% based on **2b**); (3) chromatographic purification of the bicycle **5**[12] and treatment with Pb(OAc)$_4$ (MeOH, 20 °C, 5 min; 84% yield). Overall, the carbocycle **6** was obtained in 39% yield from commercially available 1,2-cyclohexanedione.

Scheme 4



Importantly, the above approach is not limited to the construction of cyclooctanoids. Hence, a slight change in the synthetic sequence, the use of allyllithium instead of vinyllithium in the initial alkylation reaction, allowed preparation of the homologous nine-membered carbocycles (Scheme 4). The diallylation reaction led to an approximately 2:1 mixture of the *cis* and *trans* isomers, which were desilylated to give **7** and **8** in 81% combined yield. Subjecting this mixture to the RCM conditions provided the expected [4.3.1] bicyclic product **9** in 58% yield (87% based on **7**), in this case completion of the reaction requiring 15 h at rt. The oxidative bridge cleavage proceeded efficiently upon simple treatment of **9** with Pb(OAc)$_4$ (MeOH, 20 °C), affording the expected cyclononane **10** in 78% yield (37% overall yield from **1d**).

In summary, eight- and nine-membered carbocycles, which are difficult to construct by standard cyclization methods, can be expeditiously prepared in four simple steps from commercially available 1,2-cyclohexanedione by appropriately coupling a dialkylation, a cyclization, and a fragmentation reaction. The success of this approach relies on the use of a *temporary bridging connection* to decrease the entropic and enthalpic requirements of the cyclization step. Work to extend the strategy to other types of cyclization, such as the Pauson−Khand reaction, and to apply it to the synthesis of natural products containing this type of medium-sized carbocycles is now under way.

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(10) Bridge cleavage in related bicyclo[3.3.1]nonane systems has been based exclusively on Grob type of rearrangements: Hesse, M. *Ring Enlargement in Organic Synthesis*; VCH Publishers: Weinheim, 1991; p 199. See also ref 2b, p 5796.

(11) Et$_3$N, DABCO and 2,6-ditertbutylpyridine failed to promote the epimerization.

(12) Most of the *trans* isomer **3b** was recovered during chromatography.

Acknowledgment. Support of this research by the Spanish Ministry of Education and Culture under Grant PB97-0524 is gratefully acknowledged. J.R.R. thanks the Spanish Ministry of Education and Culture for a predoctoral research grant. We also thank Armando Navarro for checking the calculations and Prof. J. M. Sáa for helpful discussions.

Supporting Information Available: Relevant experimental procedures and main characterization data for **1a, 1c, 1d**, **2b**, **3b**, **5b**, **6**, **8**, **9**, and **10**. This material is available free of charge via the Internet at http://pubs.acs.org.

OL0063959