Pergamon

Tetrahedron Letters 42 (2001) 967–970

TETRAHEDRON
LETTERS

Synthesis of paddlanes having a bicyclo[1.1.1]pentane core. The consequences of olefin metathesis involving unsaturated 1,3-dicarboxylate esters of varying chain length

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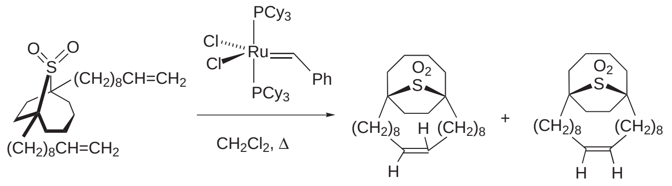
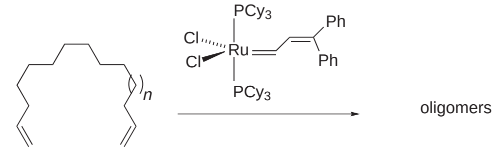
Received 20 November 2000; accepted 27 November 2000

Abstract—Described herein is the synthesis of an homologous series of bicyclo[1.1.1]pentane-1,3-dicarboxylate esters featuring ω-alkenols of differing chain length ($n=4$–8) for the purpose of evaluating their ability to undergo ring-closing metathesis/paddlane formation in the presence of Grubbs' catalyst.

We recently embarked on an investigation of the ability of doubly armed, bridged 9-thiabicyclo[4.2.1]-nonane dioxides to undergo intramolecular cyclization under olefin metathesis conditions with formation of unsaturated paddlanes.[1] This class of compounds[2] was previously found to be relatively inaccessible,[3] despite being subject to detailed theoretical scrutiny.[4] Only when $n=8$ as in **1** were monomeric end products formed (**2** and **3**, 25%). In this example as well as with its lower homologs, cyclic dimers and trimers were formed in a highly diastereoselective manner. These observations suggested that internal ruthenium/sulfonyl oxygen coordination may operate during generation of the first intermolecular double bond. Such ligation has previously been invoked for other polar groups.[5] However, unequivocal experimental proof for the intervention of chelated ruthenium carbenoids was difficult to secure. Rather, the implication was offered on the basis of the failure of **4** and similar compounds to ring close effectively,[6] and the controlled reactivity exhibited by a structurally related thiabarbaralane dioxide.[1]



1 **2** **3**



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(n=1,2)

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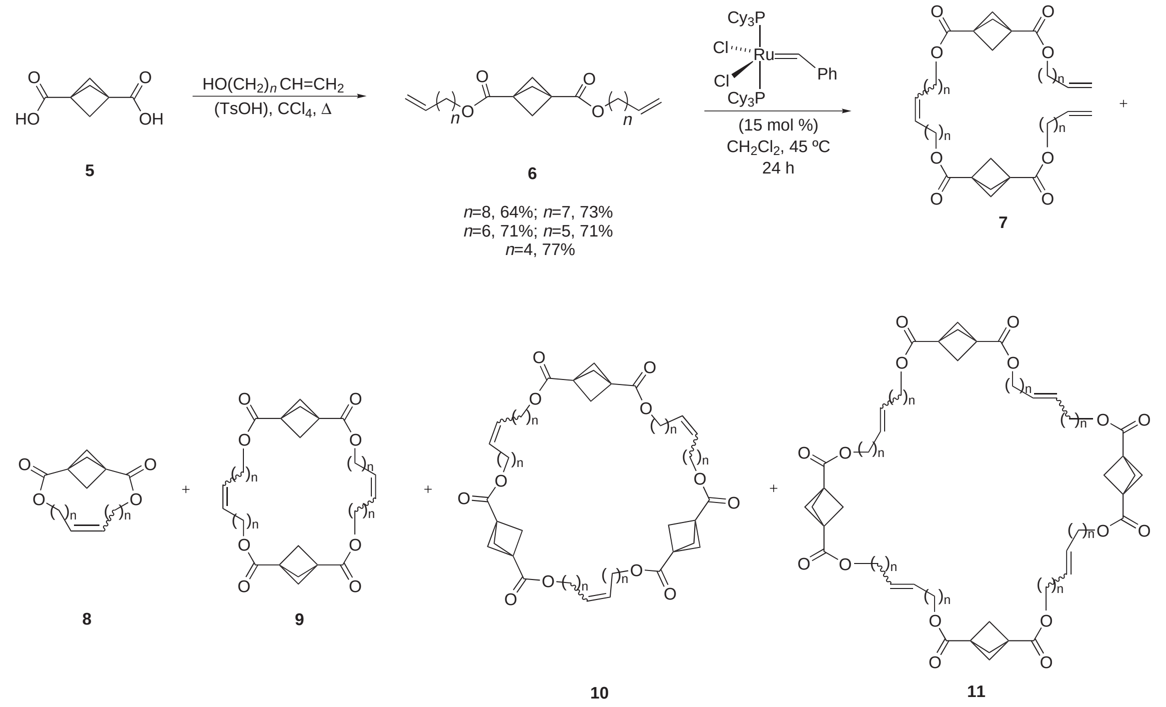
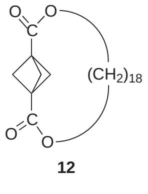


Scheme 1.

1,3-Disubstituted bicyclo[1.1.1]pentanes have in the last 15 years become widely available[7–9] via free radical addition of a variety of reagents to [1.1.1]propellane.[10] This methodology constitutes a direct means for preparing the bridgehead diacetyl derivative ($CH_3COCOCH_3$, $h\nu$), from which the dicarboxylic acid **5** can be obtained via the haloform reaction.[11] For our purposes, suitable twofold esterification of **5** was best achieved by heating with three molar equivalents of the alcohol and 0.25 equiv of *p*-toluenesulfonic acid in carbon tetrachloride[12] (Scheme 1). Recourse to the five members of the homologous series defined by **6** was expected to advance our consideration of certain features of the ring-closing metathesis (RCM) process. For example, should the first-formed ruthenium carbenoid enter presently into coordination with the carbonyl group most proximal to it,[6] cyclization will not be kinetically advantaged because the second terminal double bond remains randomly projected to an extreme level in the opposite direction. This state of affairs differs significantly from that considered for **1** where either sulfonyl oxygen is centrally positioned.

All five diesters were subjected identically to the reaction conditions specified below in order to enable direct comparison to be made. The late-stage introduction of $Pb(OAc)_4$ served the sole purpose of removing colored ruthenium impurities.[13] The product mixtures generated in this manner were directly analyzed by ^1H and ^{13}C NMR, and by electrospray mass spectrometry. The results are collected in Table 1. Under the high dilution conditions employed, the diesters having $n=7$ and 8 were found to be completely consumed. As the lengths of the chains became shorter, increasing amounts of recovered starting material and **7** were observed. This trend was reversed somewhat when the relative proportion of the ruthenium catalyst was doubled and is therefore considered to be kinetic in origin. Ring closure to generate the monomeric paddlane **8** was found to be particularly prevalent, with an expected decrease in its yield (62–17%) as the value of *n* was reduced to 5. No monomer production was seen below this chain length. These levels of direct intramolecular cyclization far exceed those observed for the lower homologs of **1**, and reflect a significant change in response to metathesis conditions. Whether this is due to those fundamental structural changes that distinguish **1** from **6**, to slight modifications in the reaction conditions, or to non-parallel mechanistic features operative during the overall RCM process is not known at present. A more detailed analysis of this matter awaits further investigation. The levels to which **8** are produced clearly suggest, however, that RCM technology may prove generally useful in accessing paddlanes of rather diverse constitution.

The crystallinity of **8** ($n=7$) permitted detailed analysis of its structure by X-ray crystallography. The ORTEP diagram shown in Fig. 1 clearly reveals the only isomer produced to feature *trans* double bond geometry. For **8** ($n=8$) two inseparable monomeric unsaturated dilactones were generated in a ratio approximating 5:2. Catalytic hydrogenation of this material over 10% Pd/C in ethanol under an atmosphere of H_2 gave rise in quantitative yield to the lone saturated product **12**, a crystalline solid of mp 58–59°C from methanol.



12

Table 1. Results of olefin metathesis experiments

Value of *n*	Recovered **6**, %	Yield of **7**, %	Global Yield of **8-11**, %	Distribution of Cyclized Products[a] **8**	**9**	**10**	**11**
8	—	—	68	92±2	7±1	0.9±0.3	—
				56	9	2	—
7	—	—	71	94±1	5±1	0.9±0.2	—
				62	7	2	—
6	15	—	61	83±0.3	16.0±0.1	0.9±0.2	—
				43	16	2	—
5	23	18	43	58±3	40±2	2.0±0.4	—
				17	24	2	—
4	36	12	40	—	67±3	—	33±3
				—	20	—	20
4[b]	8	13	57	—	94±2	—	6±2
				—	50	—	7

[a]White rows = relative amount of each observed oligomer in the product mixture normalized to 100%. Boxed rows = contribution of each oligomer to the global yield. [b]30 mol percent of catalyst used.

Finally, it should be mentioned that the intrinsic competition between intra- and intermolecular metathesis gives evidence of being amenable to reasonable levels of control despite a lack of favorable preexisting conformational features in the substrate.

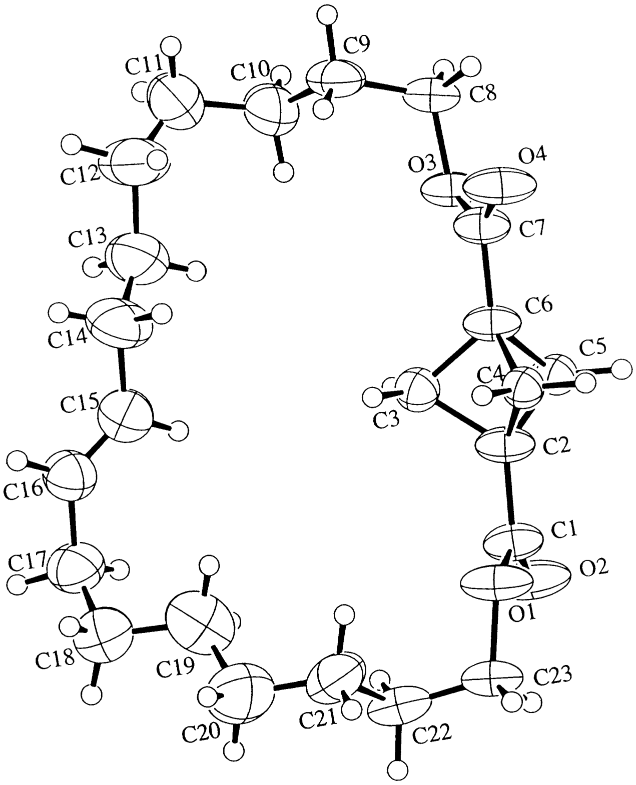


Figure 1. Computer-generated perspective drawing of **8** ($n=7$) as determined by X-ray crystallography.

Prototypical metathesis procedure

Dry CH_2Cl_2 (120 mL) was introduced via cannula into a 250 mL round-bottomed flask containing the Grubbs catalyst (43 mg, 53 mmol, 15 mol%) under an N_2 atmosphere. A solution of **7** (141 mg, 0.35 mmol) in dry CH_2Cl_2 (20 mL) was slowly introduced over 20 h by means of a syringe pump (rate = 1.67 mL/h). Immediately after the addition was started, an exterior oil bath was set at 45°C. The reaction mixture was stirred at this temperature for a total of 24 h. After cooling, lead tetraacetate (47 mg, 106 mmol) was added and stirring was maintained overnight at room temperature. The solvent was removed under reduced pressure and the product mixture was passed through a small pad of silica gel (elution with 20% ether in petroleum ether). Following solvent evaporation, the samples were analyzed directly for product composition. For individual product purification, a second, more careful chromatography was required.

Acknowledgements

Generous gifts of the Grubbs catalyst and of bicyclo[1.1.1]pentane-1,3-carboxylic acid from Dr. Craig Blankenship (Boulder Scientific Co.) and Dr. Steven Wolff (Hoffman La Roche Inc.), respectively, are gratefully acknowledged. Dr. Kari Green-Church (Ohio State Univ.) and Dr. Judith Gallucci (Ohio State Univ.) are thanked for providing the MS and X-ray data, respectively. J.M.-A. was the recipient of a fellowship award provided by the Procter and Gamble Company.

References

1. Paquette, L. A.; Fabris, F.; Tae, J.; Gallucci, J. C.; Hofferberth, J. E. *J. Am. Chem. Soc.* **2000**, *122*, 3391.
2. This generic class of compounds was originally defined by: Hahn, E. H.; Bohm, H.; Ginsburg, D. *Tetrahedron Lett.* **1973**, 507.
3. (a) Eaton, P. E.; Leipzig, B. D. *J. Am. Chem. Soc.* **1983**, *105*, 1656; (b) Warner, P.; Chen, B.-L.; Bronski, C. A.; Karcher, B. A.; Jacobson, R. A. *Tetrahedron Lett.* **1981**, *22*, 375; (c) Allen, C. F. H.; Van Allan, J. A. *J. Org. Chem.* **1953**, *18*, 882; (d) Mori, T.; Kimoto, K.; Kawanisi, M.; Nozaki, H. *Tetrahedron Lett.* **1969**, 3653; (e) Thornber, C. W. *Chem. Commun.* **1973**, 238; (f) Helder, R.; Wynberg, H. *Tetrahedron Lett.* **1973**, 4321; (g) Vögtle, F.; Koo Tze Mew, P. *Angew. Chem., Int. Ed. Engl.* **1978**, *17*, 60; (h) Wiberg, K. B.; O'Donnell, M. J. *J. Am. Chem. Soc.* **1979**, *101*, 6660; (i) Tobe, Y.; Fujita, H.; Wakaki, I.; Terashima, K.; Kobiro, K.; Kakiuchi, K.; Odaira, Y. *J. Chem. Soc., Perkin Trans. 1* **1984**, 2681; (j) Li, Y. Q.; Thiemann, T.; Mimura, K.; Sawada, T.; Mataka, S.; Tashiro, M. *Eur. J. Org. Chem.* **1998**, *1841*, 1.
4. (a) Wiberg, K. B.; Hiatt, J. E.; Burgmaier, G. *Tetrahedron Lett.* **1968**, 5855; (b) Würthwein, E.-U.; Chandrasekhar, J.; Jemmis, E. D.; Schleyer, P.; v., R. *Tetrahedron Lett.* **1981**, *22*, 843; (c) Wiberg, K. B. *Tetrahedron Lett.* **1985**, *26*, 5967.
5. Fürstner, A.; Gastner, T.; Weintritt, H. *J. Org. Chem.* **1999**, *64*, 2361 and relevant references cited therein.
6. Fürstner, A.; Langemann, K. *Synthesis* **1997**, 792.
7. (a) Wiberg, K. B.; Waddell, S. T.; Laidig, K. E. *Tetrahedron Lett.* **1986**, *27*, 1553; (b) Wiberg, K. B.; Waddell, S. T. *J. Am. Chem. Soc.* **1990**, *112*, 2194; (c) Wiberg, K. B.; McMurdie, N. *J. Am. Chem. Soc.* **1991**, *113*, 8995.
8. (a) Kaszynski, P.; McMurdie, N. D.; Michl, J. *J. Org. Chem.* **1991**, *56*, 307; (b) Kaszynski, P.; Friedli, A. C.; Michl, J. *J. Am. Chem. Soc.* **1992**, *114*, 601; (c) Obeng, Y. S.; Laing, M. E.; Friedli, A. C.; Yang, H. C.; Wang, D.; Thulstrup, E. W.; Bard, A. J.; Michl, J. *J. Am Chem. Soc.* **1992**, *114*, 9943.
9. Della, E. W.; Taylor, D. K. *J. Org. Chem.* **1994**, *59*, 2986.
10. Reviews: (a) Kascynski, P.; Michl, J. *Adv. Strain Org. Chem.* **1995**, *4*, 283; (b) Della, E. W.; Lochert, I. *J. Org. Prep. Proced. Int.* **1996**, *28*, 411; (c) Levin, M. D.; Kascynski, P.; Michl, J. *Chem. Rev.* **2000**, *100*, 169.
11. (a) Levin, M. D.; Kascynski, P.; Michl, J. *Org. Synth.* **2000**, *77*, 249; (b) Kaszynski, P.; Michl, J. *J. Org. Chem.* **1988**, *53*, 4593.
12. Hashmi, A. S. K.; Choi, J.-H.; Bats, J. W. *J. Prakt. Chem./Chem.-Ztg.* **1999**, *341*, 342.
13. Paquette, L. A.; Schloss, J. D.; Efremov, I.; Fabris, F.; Gallou, F.; Méndez-Andino, J.; Yang, J. *Org. Lett.* **2000**, *2*, 1259.