Pergamon

Tetrahedron Letters, Vol. 38, No. 30, pp. 5265-5268, 1997

0040-4039/97 $17.00 + 0.00

PII: S0040-4039(97)01160-X

Macrocyclic Oxonium Ylide Formation and Internal [2,3]-Sigmatropic Rearrangement. Catalyst Influence on Selectivity

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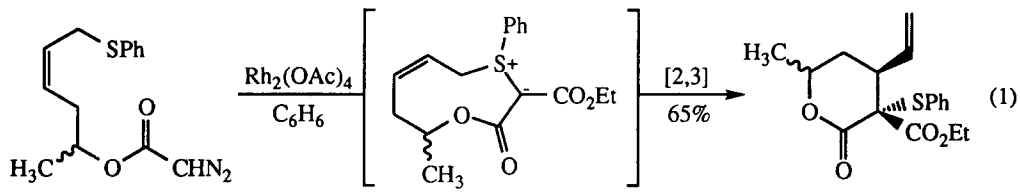
Summary: *The formation of 13-membered ring oxonium ylides and their subsequent stereocontrolled [2,3]-sigmatropic rearrangement to 10-membered ring lactones occurs in catalyst dependent competition with macrocylic cyclopropanation.* © 1997 Elsevier Science Ltd.

Ylide generation followed by [2,3]-sigmatropic rearrangement is an established, effective methodology for the construction of complex organic compounds.[1,2] Catalytic methods to achieve ylide formation from diazocarbonyl compounds have been critical to the development of this chemistry, [3,4] and for oxonium ylides these methods have been essential.[5] Generally understood to be restricted in intramolecular reactions to the formation of 5- or 6-membered rings, the largest cyclic ylide intermediate reported to have been formed is a 9-membered cyclic allylsulfonium ylide that was converted by [2,3]-sigmatropic rearrangement to lactone **2** (eq 1).[6] Similar heteroatom



(1)

1 **2**: 79:21

recognition requiring the formation of macrocyclic ylides has not been observed. Relative to oxonium ylides, sulfonium ylides are formed with comparative ease,[7,8] but oxonium ylide formation and subsequent rearrangement in intramolecular reactions is now recognized as an effective synthetic methodology.[9] We now report the formation of 13-membered ring macrocyclic oxonium ylides and their stereocontrolled rearrangement to 10-membered ring lactones.

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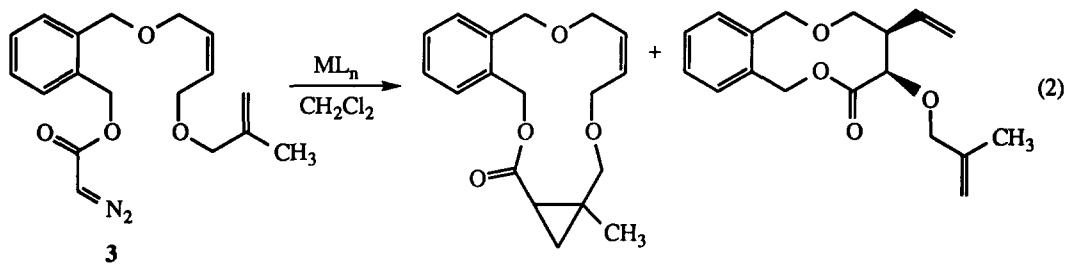
In the course of our investigations of macrolide formation by intramolecular cyclopropanation[10,11] we examined the diazo decomposition reactions of **3** which with dirhodium(II) carboxamidates underwent exclusive intramolecular addition to the terminal double



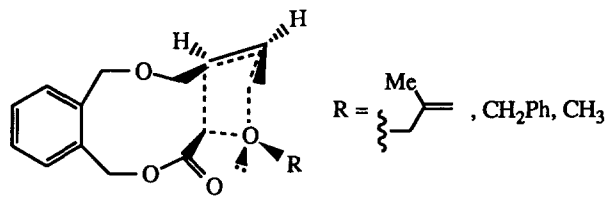
(2)

3

ML_n	*yield, %*	**4**, %	**5**, %
$Rh_2(pfb)_4$[a]	68	53	47
$Rh_2(OAc)_4$	71	94	6
$Rh_2(cap)_4$[b]	65	>99	<1
$Cu(MeCN)_4PF_6$	70	84	16

[a]pfb = perfluorobutyrate; [b]cap = caprolactamate.

bond (eq 2). However, catalysis by $Rh_2(pfb)_4$ formed a new compound whose structure was determined to be that of **5**. This product, formed in competition with macrocyclic intramolecular cyclopropanation, could have arisen only by oxonium ylide formation followed by [2,3]-sigmatropic rearrangement, the proposed transition state for which is shown (**6**). A minor component in the



6

mixture formed from catalysis by $Rh_2(OAc)_4$ and $Cu(MeCN)_4PF_6$, **5** was absent in the $Rh_2(cap)_4$ catalyzed reaction.[12] The product from intramolecular cyclopropanation of the internal *cis*-disubstituted double bond that would have resulted in a 10-membered ring lactone was not detected, nor was one from [2,3]-sigmatropic rearrangement with the methallyl group. The cis geometry of **5** is consistent with preferential formation of the threo diastereoisomer (94:6 threo:erythro) in intermolecular reactions of ethyl diazoacetate with *cis*-cinnamyl methyl ether.[5a] The trans diastereoisomer was not present in detectable quantities.

The preparation of **7a** was undertaken in order to focus more completely on ylide formation and rearrangement. Diazo decomposition of **7a** by the same series of catalysts gave the results that are described in eq 3 and Table 1. In contrast with reactions of **3**, competition occurred

between ylide formation and addition to the *cis*-disubstituted double bond: dirhodium(II) catalysts favored cyclopropanantion, while $CuPF_6$ directed reaction mainly to ylide formation/rearrangement. Dirhodium(II) caprolactamate was not effective for product formation with **7**.

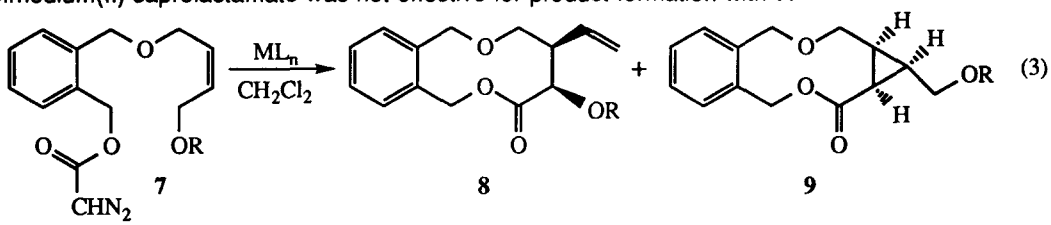
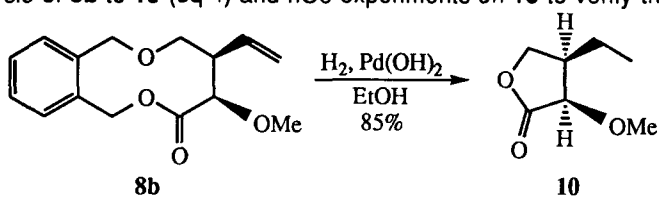


Table 1. Chemoselective macrocyclization reactions of **7a** and **7b**.[a]

Diazo compound	catalyst	yield, % [b]	product ratio, **8**:**9**	isolated yield **8**,[c]
7a (R = Bn)	$Rh_2(pfb)_4$	82	49:51	20
	$Rh_2(OAc)_4$	80	33:67	15
	$Cu(MeCN)_4PF_6$	62	74:26	29
7b (R = Me)	$Rh_2(pfb)_4$	79	77:23	31
	$Rh_2(OAc)_4$	77	81:19	33
	$Cu(MeCN)_4PF_6$	70	85:15	46

[a]Reactions were performed by the addition of **7** (1.0 mmol) in 10 mL of CH_2Cl_2 to the catalyst (1.0 mol%) in 10 mL of refluxing CH_2Cl_2 over a 5-h period. [b]Isolated yield of **8** + **9** after chromatographic separation of the catalyst. [c]Isolated yield of pure **8** after chromatographic separation from **9**.

Further structural modification of the basic framework provided the methyl ether analog **7b**. In this case catalytic diazo decomposition favored ylide formation/rearrangement with both dirhodium(II) and copper(I) catalysts (Table 1). The size of the alkoxy substituent obviously influences the chemoselectivity of the transformation, but diastereoselectivity is unaffected by either the alkoxy substituent or the choice of catalyst. The stereochemistry of **8b**[13] was established by hydrogenolysis of **8b** to **10** (eq 4) and nOe experiments on **10** to verify the relative stereochemistry



of that product. The same stereochemical relationship from [2,3]-sigmatropic rearrangement is produced with allylsulfonium ylides.[6] Investigations are underway to establish the extent to which macrocyclic ylide formation can be achieved.

Acknowledgment. Support for this research from the Robert A. Welch Foundation is gratefully acknowledged.

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13. Spectral data for compound **8b**: ^{1}HNMR (400 MHz, $CDCl_3$) δ 7.33-7.21 (comp, 2H), 5.82, (ddd, *J* = 17.4, 10.4, 8.3 Hz, 1H), 5.40 (d, *J* = 13.3 Hz, 1H), 5.32 (d, *J* = 13.3 Hz, 1H), 5.20 (ddd, *J* = 17.4, 1.7, 1.1 Hz, 1H), 5.18 (ddd, *J* = 17.4, 1.7, 1.1 Hz, 1H), 4.64 (d, *J* = 10.1 Hz, 1H), 4.79 (d, *J* = 10.1 Hz, 1H), 3.80 (d, *J* = 3.5 Hz, 1H), 3.76 (t, *J* = 10.2 Hz, 1H), 3.50 (dd, *J* = 10.2, 3.7 Hz, 1H), 3.46 (s, 3H), 3.16-3.11 (m, 1H); ^{13}CNMR (100 MHz, $CDCl_3$) δ 171.3, 136.0, 135.0, 134.6, 131.5, 128.6, 128.3, 128.0, 117.6, 80.7, 72.1, 68.7, 66.9, 59.1, 46.2.

(*Received in USA* 21 *May* 1997; *accepted* 9 *June* 1997)