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A Ru Catalyzed Divergence: Oxidative Cyclization vs Cycloisomerization of Bis-homopropargylic Alcohols

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Abstract: During the course of investigating the development of catalytic reactions involving ruthenium vinylidene intermediates, a novel divergence of reactivity was discovered. The oxidative cyclization of bis-homopropargylic alcohols with Ru(+2) complexes as catalysts and *N*-hydroxysuccinimide as oxidant, which requires formation of a ruthenium vinylidene intermediate, is complicated by the simple electrophilically initiated direct attack of the hydroxyl group on a π-complex of the alkyne and ruthenium. A catalytic system composed of CpRu[(p-$CH_3O_6H_4$)$_3$P]$_2$Cl and excess (p-$CH_3O-C_6H_4$)$_3$P directs the reaction toward the oxidative cyclization to form δ-lactones in good yields. Significantly, a simple switch of catalyst to CpRu-[(p-FC_6H_4)$_3$P]$_2$Cl redirects the reaction to a cycloisomerization to form dihydropyrans in good yields. The synthetic utility of the oxidative cyclization is illustrated by the synthesis of oviposition attractant pheromone of the mosquito *Culex pipens*. The utility of the cycloisomerization to dihydropyrans is demonstrated by an iterative process leading to the antiviral agent narbosine B. A rationale for this dramatic switch by simple ligand modification is proposed.

I. Introduction

Organometal−vinylidene complexes have been widely studied for decades.[1] The facility with which such species can be generated by direct reaction of terminal alkynes makes these species atom economical intermediates for catalytic transformations if the metal can be used catalytically. The difficulty in achieving this objective is suggested by the fact that such species have been known, but catalytic reactions remain almost unknown. Some years ago, we initiated programs toward developing catalytic reactions involving ruthenium vinylidene complexes as reactive intermediates and reported a ruthenium-catalyzed two-component coupling of allyl alcohols and terminal alkynes to form β,γ-unsaturated ketones invoking such complexes as the key reactive intermediates.[2,3] In these studies we noted the electrophilic nature of such ruthenium−vinylidene complexes.

Because of this electrophilic nature, ruthenium−vinylidene complexes generated from homopropargylic and bis-homopropargylic alcohols form stable cyclic oxacarbene complexes.[4,5] Although these complexes are reported to be inert to chemical reactions,[6] our continuing interest in this area and the potential synthetic utility of oxygen-heterocycles prompted us to investigate catalytic reactions by using such oxacarbene complexes as reactive intermediates. Recently, we successfully developed a novel oxidative cyclization of homopropargylic alcohols to form γ-butyrolactones, using *N*-hydroxysuccinimide as a mild oxidant.[7] In an effort to extend the scope of the reaction, we turned our attention to bis-homopropargylic alcohols.

An interesting series of molybdenum- and tungsten-mediated cycloisomerizations of homopropargylic and bis-homopropargylic alcohols to dihydrofurans and dihydropyrans has been reported by McDonald et al.[8] In these studies, bis-homopropargylic alcohols are converted into dihydropyrans generally in moderate yield.[8a,b] Recent studies from the McDonald group show much improved results in terms of yield, but typically require photolysis at elevated temperatures as well as high catalyst loading (~25%).[8c,d] In considering the oxidative cyclization of bis-homopropargylic alcohols to valerolactones, we

(1) For reviews, see: Bruce, M. I.; Swincer, A. G. *Adv. Organomet. Chem.* **1983**, *22*, 59. Bruce, M. I. *Chem. Rev.* **1991**, *91*, 197. Bruneau, C.; Dixneuf, P. H. *Acc. Chem. Res.* **1999**, *32*, 311.
(2) Trost, B. M.; Kulawiec, R. J. *J. Am. Chem. Soc.* **1992**, *114*, 5579. Trost, B. M.; Dyker, G.; Kulawiec, R. J. *J. Am. Chem. Soc.* **1990**, *112*, 7809.
(3) For other examples of catalytic reactions of terminal acetylenes via vinylidene intermediates, see: Mahé, R.; Sasaki, Y.; Bruneau, C.; Dixneuf, P. H. *J. Org. Chem.* **1989**, *54*, 1518. Wakatsuki, Y.; Yamazaki, H.; Kumegawa, N.; Satoh, T.; Satoh, J. Y. *J. Am. Chem. Soc.* **1991**, *113*, 9604. Murakami, M.; Ubukata, M.; Ito, Y. *Tetrahedron Lett.* **1998**, *39*, 7361. Merlic, C. A.; Pauly, M. E. *J. Am. Chem. Soc.* **1996**, *118*, 11319. Gemel, C.; Trimmel, G.; Slugovc, C.; Kremel, S.; Mereiter, K.; Schmid, R.; Kirchner, K. *Organometallics* **1996**, *15*, 3998.
(4) Bruce, M. I.; Swincer, A. G.; Thomson, B. J.; Wallis, R. C. *Aust. J. Chem.* **1980**, *33*, 2605.
(5) For a review on the synthesis and chemistry of cyclic metal-complexed oxacarbene complexes, see: Weyerhausen, B.; Dotz, K. H. *Eur. J. Inorg. Chem.* **1999**, 1057. For a review on reactions that use such a concept, see: McDonald, F. E. *Chem. Eur. J.* **1999**, *5*, 3103.
(6) Davies, G.; McNally, J. P.; Smallridge, A. *J. Adv. Organomet. Chem.* **1990**, *30*, 1.
(7) Trost, B. M.; Rhee, Y. H. *J. Am. Chem. Soc.* **1999**, *121*, 11680.
(8) (a) For example, see: McDonald, F. E.; Bowman, J. L. *Tetrahedron Lett.* **1996**, *37*, 4675. (b) McDonald, F. E.; Zhu, H. Y. H. *J. Am. Chem. Soc.* **1998**, *120*, 4246. (c) McDonald, F. E.; Reddy, K. S.; Diaz, Y. *J. Am. Chem. Soc.* **2000**, *122*. 4304. (d) While this manuscript was in preparation, a new cycloisomerization process was reported which needs 10% tungsten catalyst. Although this result represents considerable improvement in terms of catalyst loading, the scope of such a process has yet to be determined: McDonald, F. E.; Reddy, K. S. *J. Organomet. Chem.* **2001**, *617*, 444.

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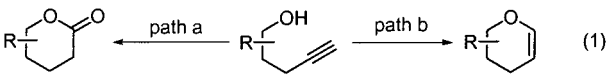
Table 1. Optimization of Oxidative Cyclization and Cycloisomerization[a]

entry	Ru complex (mol %)	ligand (mol %)	**4** (mol %)	time (h)	conversion (%)	yield **6**[a] (isolated yield)	yield **7**[b] (isolated yield)
1	**9a** (10%)	**2a** (20%)	300[c]	15	100	20%	33%
2	**9a** (10%)	**2a** (40%)	300[c]	17	100	25%	31%
3	**9a** (10%)	**2a** (60%)	300[c]	25	80	17%	24%
4	**9b** (10%)	**2b** (40%)	300[c]	20	100	38% (34%)	40 (35%)
5	**9c** (10%)	**2c** (40%)	300[c]	17	100	60% (57%)	20% (17%)
6	**9d** (10%)	**2d** (40%)	300[c]	17	100	51%	23%
7	**9e** (10%)	**2e** (40%)	300[c]	17	100	19% (16%)	57% (52%)
8	**9f** (10%)	**2f** (40%)	300[c]	26	91	13%	56%
9	**9g** (10%)	**2g** (40%)	300[c]	26	81	9%	53%
10	**9c** (10%)	**2c** (40%)	450[c]	20	100	(65%)	(11%)
11	**9c** (10%)	**2c** (40%)	600[c]	23	100	(69%)	(7%)
12	**9c** (10%)	**2c** (40%)	1000[c]	28	46	(30%)	(trace)
13	**9c** (5%)	**2c** (20%)	600[d]	28	73	(45%)	(6%)
14	**9e** (10%)	**2e** (40%)	200[d]	17	100	(11%)	(60%)
15	**9e** (7.5%)	**2e** (30%)	100[d]	20	100	(7%)	(61%)
16	**9e** (5%)	**2e** (20%)	50[d]	25	99	(4%)	(64%)
17	**9e** (5%)	**2e** (20%)	25[d]	25	84	(5%)	(53%)

[a] All reactions were run at 0.4 M bis-homopropargylic alcohol in DMF at 85 °C with 200 mol % $NaHCO_3$ unless otherwise noted. [b] Yield determined by gas chromatography with *n*-tetradecane as an internal standard, except where indicated it was an isolated yield. [c] *N*-Hydroxysuccinimide used. [d] Preformed sodium salt of *N*-hydroxysuccinimide used, and sodium bicarbonate was not added.

uncovered an unusual flexibility to form either valerolactones (eq 1, path a) or dihydropyrans (eq 1, path b) by simple ligand

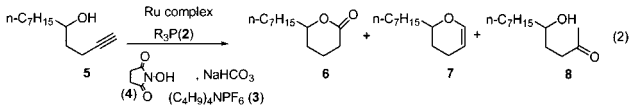


(1)

variation with the ruthenium-catalyzed process.

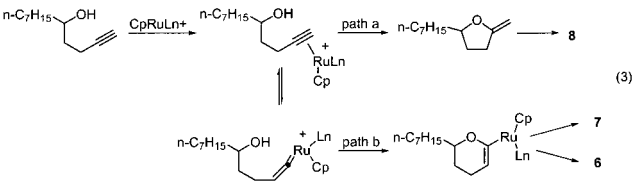
II. Results

A. Optimization of Reaction Conditions. Extrapolation of the oxidative cyclization to six-membered rings was not straightforward. Ruthenium (+2) complexes are known to initiate addition of oxygen nucleophiles to alkynes.[9] Homopropargylic alcohols would not be so prone to such a competing event, because it would require a 4-exo transition state. On the other hand, bis-homopropargylic alcohols should be able to undergo the related 5-exo cyclization more readily.[10] Indeed, this fear was justified as illustrated in the preliminary attempt shown in eq 2. By using the conditions optimized for formation



(2)

of butyrolactones, 10 mol % CpRu(COD)Cl (**1**), 15 mol % tris (2-furyl)phosphine (**2a**), 30 mol % tetra-*n*-butylammonium hexafluorophosphate (**3**), 3 equiv of *N*-hydroxysuccinimide (**4**), and 2 equiv of sodium bicarbonate in 7:1 dimethylformamide (DMF)/water at 85 °C gave an approximately coequal mixture of lactone **6**,[11] dihydropyran **7**,[12] and ketone **8**[13] from bis-homopropargylic alcohol **5**.[14] The latter presumably arises via 5-exo cyclization of the alcohol onto the alkyne followed by hydrolysis (eq 3, path a);[15] whereas, the two former compounds,



(3)

6 and **7**, arise via the desired vinylidene complexes (eq 3, path b).

Although removing water eliminated the formation of methyl ketone **8**, the combined yield of **6** and **7** was not much affected. Presumably, path a is still occurring but the resultant enol ether simply decomposes in the absence of water. On the other hand, increasing the amount of phosphine **2a** to 40 mol % under the anhydrous condition had a significant increase in the combined amount of **6** and **7**. As a result we switched to use of complexes of type **9**.[16,17]

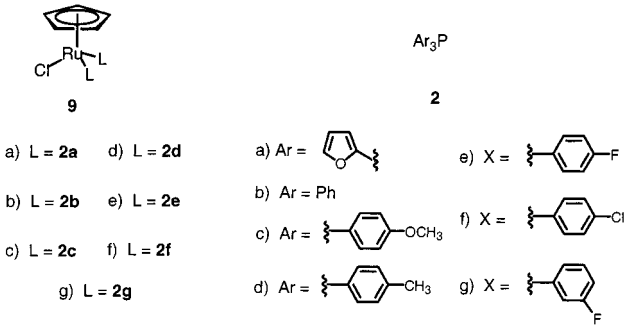


Table 1 summarizes some of our efforts to optimize formation of the six-membered ring products. Increasing the amount of excess ligand to 60 mol % (entry 3) slowed the reaction

(9) (a) Mitsudo, T.; Hori, Y.; Yamakawa, Y.; Watanabe, Y. *J. Org. Chem.* **1987**, *52*, 2230. (b) Neveux, M. I.; Seiller, B.; Hagedorn, F.; Bruneau, C.; Dixneuf, P. H. *J. Organomet. Chem.* **1993**, *451*, 133.

(10) (a) For such a pathway in a Pd-catalyzed cyclization, see: Wang, Z.; Lu, X. *J. Org. Chem.* **1996**, *61*, 2254. (b) This exo-mode cyclization has been addressed in tungsten-catalyzed cycloisomerization of bis-homopropargylic alcohols. See ref 8c.

(11) Mino, T.; Masuda, S.; Nishio, M.; Yamashita, M. *J. Org. Chem.* **1997**, *62*, 2633.

(12) All new compounds were fully characterized.

(13) Vaskan, R. N.; Kovalev, B. G. *Zh. Org. Khim.* **1975**, *11*, 1818.

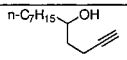
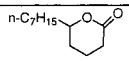
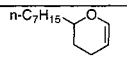
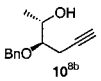
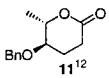
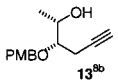
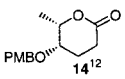
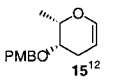
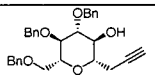
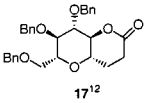
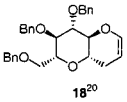
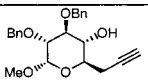
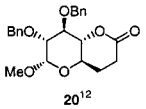
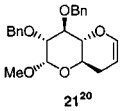
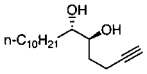
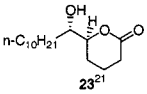
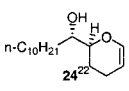
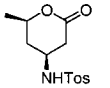
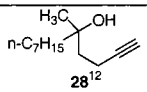
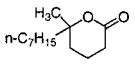
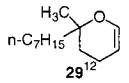
(14) Yamaguchi, M.; Nobayashi, Y.; Hirao, I. *Tetrahedron Lett.* **1983**, *24*, 5121.

(15) This result could be alternatively explained by simple hydration of ruthenium−alkyne complex with water. However, this possibility was excluded by the experimental result with 1-octyne, which did not produce the corresponding ketone under the same reaction condition.

(16) Complex **1** forms catalysts **9** in the presence of excess amount of the corresponding phosphines **2**. In fact, the use of 10% complex **1** with 60% ligand **2a** gave a result similar to entry 1 (Table 1). However, because of the low yield in the preparation of complex **1**, the use of in situ-generated catalyst **9** was not investigated further. For the synthesis and the use of complex **1**, see: Albers, M. O.; Robinson, D. J.; Shaver, A.; Singleton, E. *Organometallics* **1986**, *5*, 2199.

(17) For the synthesis of these types of Ru complexes, see: Hartwig, J. F.; Bhandari, S.; Rablen, P. R. *J. Am. Chem. Soc.* **1994**, *116*, 1839.

Table 2. Examples

Entry	Substrate	Method[a]	Time	Conversion	Lactone Isolated yield		Dihydropyran Isolated yield	
1a	 **5**[14]	A	23h	>99%	 **6**[11]	69%	 **7**[12]	7%
1b		C	25h	99%		4%		64%
2a	 **10**[8b]	A	24h	97%	 **11**[12]	63%	 **12**[8b]	6%
2b		B	18h	100%		70%		5%
2c		C	24h	100%		5%		72%
3a	 **13**[8b]	A	24h	93%	 **14**[12]	58%	 **15**[12]	8%
3b		B	18h	100%		67%		7%
3c		C	24h	100%		6%		67%
4a	 **16**[19]	A	26h	100%	 **17**[12]	65%	 **18**[20]	7%
4b		C	26h	99%		5%		68%
5a	 **19**[19]	A	22h	100%	 **20**[12]	51%	 **21**[20]	6%
5b		C	19h	100%		6%		70%
6a		A	24h	70%		48%		9%
6b	 **22**[12]	B	25h	98%	 **23**[21]	64%	 **24**[22]	8%
6c		C	25h	94%		5%		62%
6d		D	22h	100%		6%		65%
7a	 **26**[12]	A	24h	No Rxn[b]		- - - -	 **27**[12]	- - - -
7b		C	22h	75%[c]		- - - -		46% (61%)[d]
8a	 **28**[12]	A	25h	No Rxn		- - -	 **29**[12]	- - - -
8b		E	25h	75%		- - - -		44% (59%)[d]

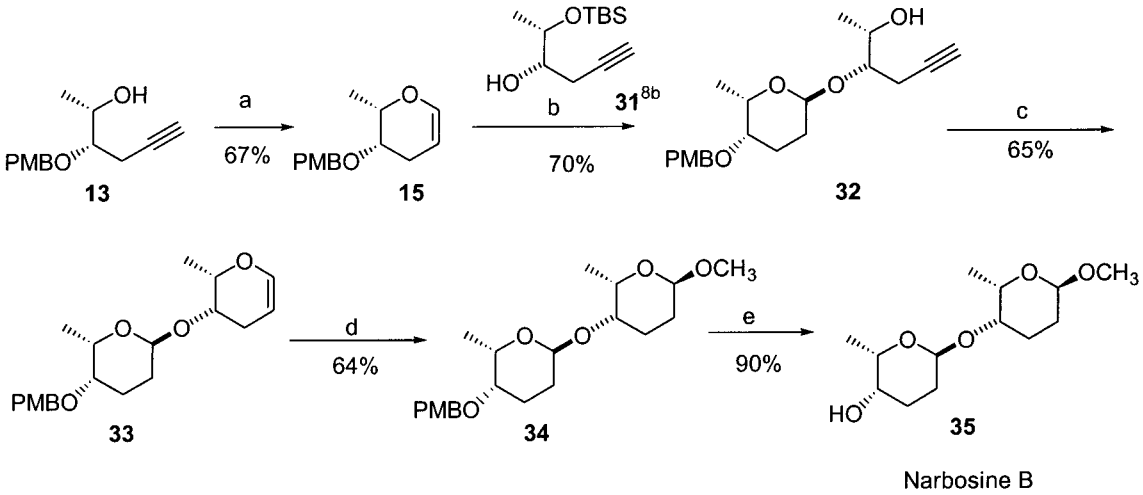
[a] Method A: 10 mol % **9c**, 40 mol % **2c**, 30 mol % **3**, 6 equiv of **4**, 2 equiv of $NaHCO_3$. Method B: 15mol % **9c**, 60 mol % **2c**, 45 mol % **3**, 6 equiv of **4**, 2 equiv of $NaHCO_3$. Method C: 5 mol % **9e**, 20 mol % **2e**, 15 mol % **3**, 50 mol % **4** sodium salt. Method D: 7.5 mol % **9e**, 30 mol % **2e**, 23 mol % **3**, 1 equiv of **4** sodium salt. Method E: 10 mol % **9e**, 40 mol % **2e**, 30 mol % **3**, 2 equiv of **4** sodium salt. [b] *p*-$TsNH_2$ was obtained (~10%). [c] *p*-$TsNH_2$ was obtained (a trace amount). [d] Yield based on recovered starting material.

considerably. A significant improvement arises by switching to triphenylphosphine as the ligand (entry 4). Placing an electron-donating substituent[18] in the para position not only retained good yields but tilted the ratio to favor the lactone **6** (entries 5 and 6). Conversely, electron-withdrawing substituents in the para (entries 7 and 8) or meta (entry 9) position[18] favored the formation of the dihydropyran **7**. A further increase in the amount of lactone is observed by increasing the amount of *N*-hydroxysuccinimide (entries 10 and 11) but too much has a strong negative impact on conversion (entry 12). Decreasing the amount of catalyst maintained the same **6**:**7** ratio but with incomplete conversion (entry 13). On the other hand, decreasing the amount of *N*-hydroxysuccinimide (used as its preformed sodium salt) increased the amount of dihydropyran compared with lactone while maintaining good yields (entry 14). Significantly, decreasing the amount of catalyst as well as sodium salt of **3** maintained good yields and **6**:**7** ratios (entries 15−17). Thus, we adopted the conditions of entry 10 for the synthesis of lactones and those of entry 16 for dihydropyrans.

B. Scope and Limitation. With the optimized conditions in hand, we tested several bis-homopropargylic alcohols to determine the scope and limitation of the reaction. As summarized in Table 2, formation of dihydropyrans generally required lower catalyst loading than those for lactone formation, as low as 5 mol % for complete conversion. In entry 6c vs 6d, an increased catalyst loading from 5 mol % to 7.5 mol % did increase the conversion from 94% to quantitative, but the isolated yield of dihydropyran increased very little. On the contrary, yields of lactones almost invariably increased by running the reactions with 15 mol % compared to 10 mol % (entries 2a, 3a and 6a vs 2b, 3b, and 6b). The reactions show excellent chemoselectivity. In entry 6, only the six-membered ring products formed. The

(18) For quantitative data for electron density of phosphine ligands, see: Tolman, C. A. *Chem. Rev.* **1977**, *77*, 313.

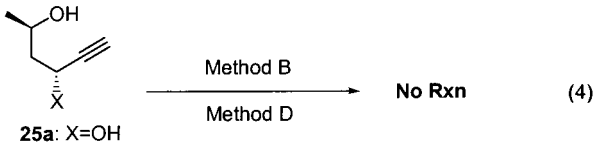
Scheme 1. A Synthesis of Narbosine B



[a] See Table 2, entry 3c. [b] (*i*) TsOH, $PhCH_3$, r.t., (*ii*) TBAF, THF, r.t. [c] Method D, Table 2. [d] CSA, CH_3OH, r.t. [e] DDQ, CH_2Cl_2, H_2O, r.t.

yield for entries 2c and 3c are considerably higher than the only ones reported for a related process that uses stoichiometric amounts of tungsten to cycloisomerize to dihydropyrans.[8b]

Substrates bearing heteroatom substituent at propargylic position such as **26** are particularly interesting because these types of compounds form allenylidene complexes with the concomitant elimination of propargylic substituents.[23] In fact, propargylic alcohol derivatives **25a**−**25c** failed to produce the corresponding dihydropyrans and valerolactones under both conditions (eq 4). In all tests, only unreacted starting materials

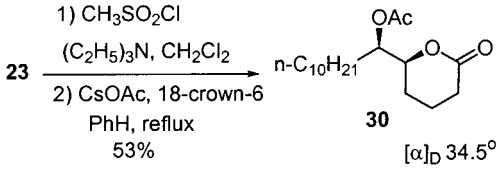


(4)

25a: X=OH
25b: X=OBn
25c: X=OTIPS

were recovered. In substrate **25b** benzyl alcohol was isolated (~10% yield). Unlike **25**, substrate **26** provided the desired dihydropyran **27** in moderate yield under cycloisomerization; whereas it remained unreactive under oxidative cyclization. In both cases, *p*-toluenesulfonamide was obtained (~10% for entry 7a, a trace amount for entry 7b). Another interesting disparity is seen with tertiary alcohol **28**. Although oxidative cyclization failed to produce the corresponding lactone, cycloisomerization with 10% catalyst produced the dihydropyran **29** in modest yield. This result is surprising because tertiary alcohols previously proved to be the best substrates for oxidative cyclization of homopropargylic alcohols.[7]

Several of the examples already provide interesting and useful structural motifs. For example, dihydropyrans **12** and **15** or their lactones **11** and **14** can be converted to the deoxysugars D-amicetose[24] and D-rhodinose,[25] which are constituents of more complex natural products. Compounds **17**, **18**, **20**, and **21** can serve in the construction of polyethers represented by the brevetoxins, ciguatoxins, dactomelynes, maitotoxins, etc.[20] The synthesis of compound **27** gives a novel access to aminosugars.[26] The oviposition attractant pheromone of the mosquito *Culex pipens fatigans* **30**[27] was synthesized from the lactone **23** as shown in eq 5 as demonstrated previously.[21,28a] The absolute

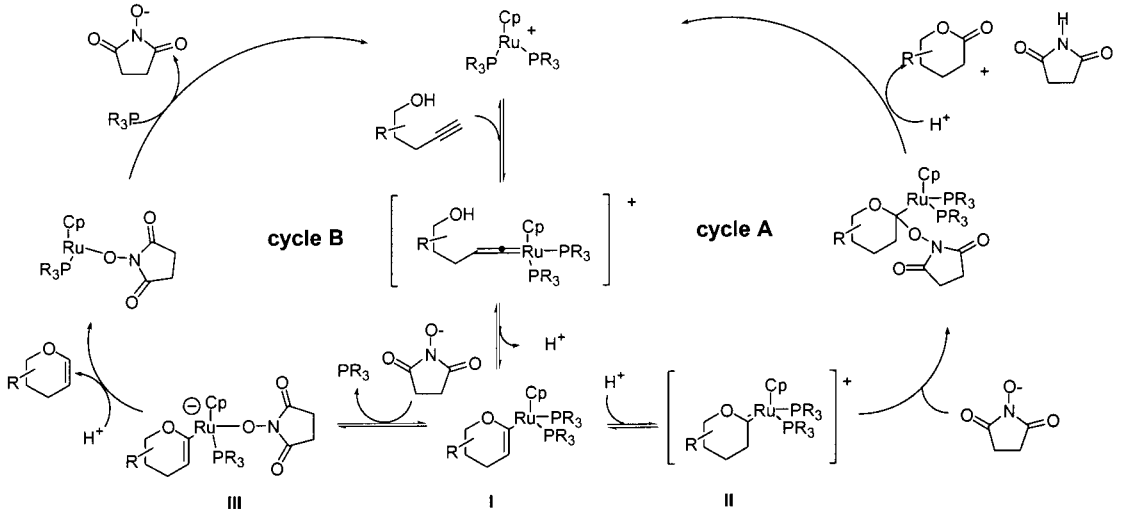


(5)

stereochemistry derived from an asymmetric dihydroxylation of an E-olefin precursor and the ee was established as 93% by the comparison of optical rotation for both **23** and the natural product itself.[28b] Analogous to the work of McDonald et al., an iterative process can be performed.[8b] Thus, a synthesis of narbosine B, an antiviral secondary metabolite from *Streptomyces*,[29] was performed (see Scheme 1). Compound **32** formed as a single stereoisomer and underwent cycloisomerization to glycal **33** under our standard protocol. Acid-catalyzed addition of methanol to this compound produced acetal **34** in 64% yield accompanied by 9% of the epimer. For analytical purposes, the major isomer was separated and reacted with DDQ to provide **35** as a single anomer, whereas previously it was only isolated as an anomeric mixture.[29]

(19) Leeuwenburgh, M. A.; Litjens, R. E. J. N.; Codee, J. D. C.; Overkleeft, H. S.; van der Marel, G. A.; van Boom, J. H. *Org. Lett.* **2000**, *2*, 1275.
(20) Van Boom, J. H.; Leeuwenburgh, M. A.; Overkleeft, H. S.; van der Marel, G. A. *Synlett* **1997**, 1263.
(21) Depezay, J.-C.; Gravier-Pelletier, C.; Le Merrer, Y. *Tetrahedron* **1995**, *51*, 1663.
(22) Jefford, C. W.; Jaggi, D.; Boukouvalas, J. *Tetrahedron Lett.* **1986**, *27*, 4011.
(23) (a) For a general review on the formation of allenylidene complexes, see: Bruce, M, I. *Chem. Rev.* **1991**, *91*, 197. (b) For a catalytic reaction using such complexes as reactive intermediates, see: Trost, B. M.; Flygare, J. A. *J. Am. Chem. Soc.* **1992**, *114*, 5476.
(24) For some recent syntheses, see: Noecker, L. A.; Martino, J. A.; Foley, P. J.; Rush, D. M.; Giuliano, R. M.; Villani, F. J., Jr. *Tetrahedron: Asymmetry* **1998**, *9*, 203. Pedersen, C.; Jensen, H. S. *Acta Chem. Scand.* **1994**, *48*, 222. Lajsic, S.; Miljkovic, D.; Cetkovic, G. *Carbohydr. Res.* **1992**, *233*, 261.
(25) For more recent syntheses, see: Rohr, J.; Wohlert, S.-E.; Oelkers, C.; Kirschning, A.; Ries, M. *Chem. Commun.* **1997**, 973. Sobti, A.; Sulikowski, G. A. *Tetrahedron Lett.* **1995**, *36*, 4193.
(26) For a review on the synthesis of aminosugars, see: Hauser, F. M.; Ellenberger, S. R. *Chem. Rev.* **1986**, *86*, 35.
(27) (a) Lin, G.; Xu, H.; Wu, B.; Guo, G.; Zhou, W. *Tetrahedron Lett.* **1985**, *26*, 1233. (b) Machiya, K.; Ichimoto, I.; Kirihata, M.; Ueda, H. *Agric. Biol. Chem.* **1985**, *49*, 643.
(28) (a) Kotuski, H.; Kadota, I.; Ochi, M. *J. Org. Chem.* **1990**, *55*, 4417. (b) Eliel, E. L.; Ko, K.-Y. *J. Org. Chem.* **1986**, *51*, 5353.
(29) Henkel, T.; Breiding-Mack, S.; Zeeck, A.; Grabley, S.; Hammann, P. E.; Hutter, K.; Till, G.; Thiericke, R.; Wink, J. *Liebigs Ann. Chem.* **1991**, 575.

Scheme 2. Mechanistic Rationale

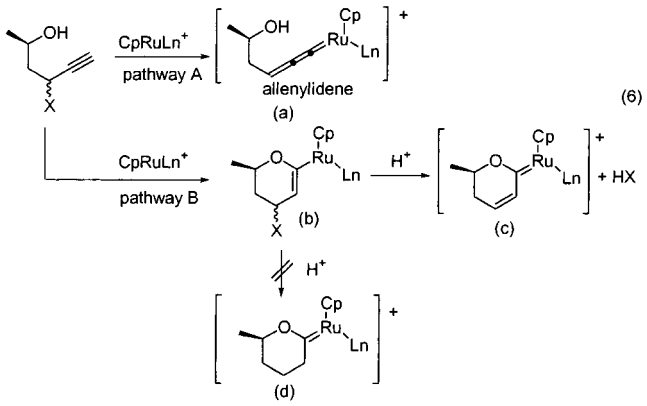


III. Mechanism

The reactions of bis-homopropargylic alcohols show striking differences from those of homopropargylic alcohols. Ru(II) activates the *trans*-addition of oxygen nucleophile to alkynes.[9] In this pathway ruthenium simply coordinates to alkynes and promotes the addition of the nucleophile, as mentioned previously. Phosphine in excess to Ru is needed to divert the reaction from such reactions to the formation of the key vinylidene complexes.

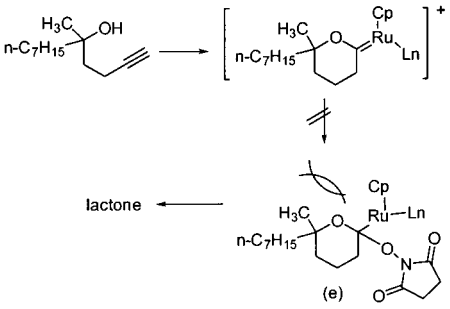
Scheme 2 rationalizes the divergent behavior. Cycle A is favored by more electron-rich ligands and larger excess of ligands; whereas, cycle B is favored by less electron-rich ligands and lower amounts of ligands. Thus, a ligand possessing suitable electronic properties to facilitate formation of the pivotal intermediate I is needed. If it is electron rich enough, it can promote protonation at carbon to form the oxacarbene complex II leading to lactone. On the other hand, if it is less electron rich, ligand exchange to form an anionic complex III may occur and allow simple protonation of the C-bound ligand to liberate the dihydropyran. The formation of dihydropyran looks particularly intriguing because this transformation has been investigated by others with no success in the presence of ruthenium complexes and conventional (noncoordinating) bases.[30] Our extensive effort to substitute other bases for *N*-hydroxysuccinimide also failed to give any dihydropyrans.[31] This result indeed supports the mechanistic rationale; simple protonation of complex I occurs only at the carbon to generate complex II. Therefore, the use of coordinating bases to promote ligand exchange in the cycloisomerization pathway seems to be crucial.

In substrates **25** and **26**, the elimination of propargylic substituents turned out to be very facile. As depicted in eq 6, such elimination could be explained either by the formation of allenylidene complexes a (pathway a, eq 6), or the formation of plausible intermediate c after the formation of complex b (pathway b, eq 6).[32] In the oxidative cyclization, such elimination will be promoted by excess protonic acid (*N*-hydroxysuccinimide). In the cycloisomerization, on the other hand, the leaving group capability of the propargylic substituent plays a role. In substrate **25**, the elimination still predominates because of the presence of better leaving groups. Presumably, such a process is promoted by the coordination of Lewis acidic ruthenium complexes. In **26**, the desired cycloisomerization overrides the elimination because of the presence of a poorer leaving group (which is also a poor Lewis base).



(6)

The disparity with tertiary alcohol **28** can be explained by the activating effect of electron-poor phosphine ligand **2e** over **2c** in the formation of complex I (Scheme 2), as well as the steric interaction in forming intermediate (e) in oxidative cyclization, as described in eq 7. This type of steric interaction



(7)

is not seen in cycloisomerization.[33]

(30) For example, see 6: Also see, McDonald, F. E.; Bowman, J. L. *J. Org. Chem.* **1998**, *63*, 3680.

(31) Examples include organic bases (triethylamine, 2,6-di-*tert*-butylamine, proton sponge) and inorganic bases ($NaHCO_3$, Na_2CO_3, sodium *p*-nitrophenoxide, NaOMe, NaOH). On the other hand, other *N*-hydroxyimides (such as *N*-hydroxyphthalimide, *N*-hydroxymaleimide) also showed considerable conversion.

(32) McDonald, F. E.; Gleason, M. M. *J. Am. Chem. Soc.* **1996**, *118*, 6648.

IV. Summary

In this article, we described a divergent ruthenium-catalyzed reaction from bis-homopropargylic alcohols that provides a convenient access to either dihydropyrans or valerolactones. Unlike homopropargylic alcohols, the reactions of bis-homopropargylic alcohols required the use of excess phosphines to avoid the undesired exo-cyclization pathway. Furthermore, either cycloisomerization to dihydropyrans or oxidative cyclization to δ-valerolactones may be performed. The divergence described here is remarkable because it derives only by choice and amount of phosphine ligands, a flexibility not previously observed.

V. Experimental

1. General Procedures for the Synthesis of Dihydropyrans. 1.a. Preparation of Dihydropyran 7 from Alcohol 5. By using method C in Table 2, a mixture of alcohol **5** (140 mg, 0.768 mmol), catalyst **9e** (32 mg, 0.038 mmol), ligand **2e** (49 mg, 0.15 mmol), **4** sodium salt (53 mg, 0.38 mmol), and tetra-*n*-butylammonium hexafluorophosphate (39 mg, 0.10 mmol) in DMF (1.9 mL, 0.4 M) was placed in a preheated oil bath at 85 °C and stirred at that temperature under N_2 for 25 h. The reaction mixture was cooled to room temperature and diluted with ether (30 mL) and washed with water (2 × 10 mL). The aqueous layer was extracted with ether (2 × 25 mL). The organic layers were combined, dried over $MgSO_4$, and concentrated. The residual oil was purified by column chromatography (with deactivated silica gel, eluted with pet-ether/EtOAc 20:1) to provide dihydropyran **7** (91 mg, 0.50 mmol) as clear oil (64% yield) R_f 0.70 (pet-ether/EtOAc 20:1).

IR (neat film): ν 2928, 2856, 1730, 1461, 1260, 1121, 1033 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz): δ 6.36(d, J = 5.7 Hz, 1H), 4.65(m, 1H), 3.84(m, 1H), 1.85−2.10(m, 2H), 1.15−1.80(m, 14H), 0.88(t, J = 6.5 Hz, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 143.8, 100.3, 75.2, 35.3, 31.8, 29.6, 29.3, 27.8, 25.3, 22.7, 19.9, 14.1. HRMS: Calcd for $C_{12}H_{22}O$ (M^+): 182.1671. Found: 182.1673.

Further elution (with pet-ether/EtOAc 4:1) provided unreacted starting material 5 (∼1 mg) and the lactone **6** as clear oil (6 mg, 0.03 mmol, 4% yield).

1.b. Preparation of Dihydropyran 18 from Alcohol 16. With the same method, a mixture of **16** (238 mg, 0.503 mmol), ruthenium catalyst **9e** (21 mg, 0.025 mmol), phosphine ligand **2e** (32 mg, 0.10 mmol), **4** sodium salt (35 mg, 0.25 mmol), and tetra-*n*-butylammonium hexafluorophosphate (29 mg, 0.076 mmol) in DMF (1.3 mL, 0.4M) was placed in a preheated oil bath at 85 °C and stirred at that temperature for 26 h. The reaction mixture was cooled to room temperature. DMF was removed under reduced pressure, and the reaction mixture was purified directly with column chromatography (with deactivated silica gel, eluted with pet-ether/EtOAc 20:1) to give the title compound **6b** as clear oil (162 mg, 0.344 mmol, 68% yield). The spectral data are in full accord with the reported value.[20] $[\alpha]_D$ 50.5 (*c* 2.10, $CHCl_3$). R_f 0.75 (pet-ether/EtOAc 10:1).

IR (neat film): ν 3064, 3030, 2859, 1649, 1497, 1454, 1362, 1320, 1238, 1209, 1107, 1068 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz): 7.11−7.41(m, 15H), 6.39(d, J = 5.6 Hz, 1H), 4.99(d, J = 11.0 Hz, 1H), 4.90(d, J = 10.7 Hz, 1H), 4.86(d, J = 10.7 Hz, 1H), 4.79(d, J = 11.0 Hz, 1H), 4.71(m, 1H), 4.62(d, J = 12.2 Hz, 1H), 4.54(d, J = 12.2 Hz, 1H), 3.40−3.60(m, 7H), 2.40(m, 1H), 2.20(m, 1H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 142.8, 138.7, 138.1, 137.9, 128.4, 128.3, 127.9, 127.8, 127.7, 127.6, 127.5, 98.3, 84.2, 79.1, 78.8, 77.4, 75.2, 74.9, 73.5, 72.2, 68.9, 26.7.

Further elution (with pet-ether/EtOAc :1) provided starting material (2 mg, 0.005 mmol, 1%) and lactone **17** (17 mg, 0.026 mmol, 5%).

2. General Procedures for the Synthesis of Valerolactones. 2.a. Preparation of Valerolactone 6 from Alcohol 5. By using method A in Table 2, a mixture of alcohol **5** (135 mg, 0.742 mmol), catalyst **9c** (67 mg, 0.074 mmol), ligand **2c** (104 mg, 0.296 mmol), *N*-hydroxysuccinimide (511 mg, 4.44 mmol), sodium bicarbonate (124 mg, 1.48 mmol), tetra-*n*-butylammonium hexafluorophosphate (86 mg, 0.222 mmol) in DMF (1.9 mL, 0.4M) was placed in a preheated oil bath at 85 °C and stirred at that temperature under N_2 for 23 h. The reaction mixture was cooled to room temperature and diluted with ether (30 mL) and washed with water (2 × 10 mL). The aqueous layer was extracted with ether (2 × 25 mL). The organic layers were combined, dried over $MgSO_4$, and concentrated. The residual oil was purified by column chromatography (with deactivated silica gel, eluted with pet-ether/EtOAc 20:1) to provide dihydropyran **7** (10 mg, 0.052 mmol, 7%). Further elution (with pet-ether/EtOAc 4:1) provided a trace amount of starting material (<1 mg) and valerolactone **6** (101 mg, 0.509 mmol) as clear oil (69% yield). The spectral data are in full accord with the reported value.[11] R_f 0.50 (pet-ether/EtOAc 7:1).

IR (neat film): ν 2928, 2857, 1736, 1465, 1378, 1342, 1241, 1178, 1046 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz): δ 4.26(m, 1H), 2.41−2.62 (m, 2H), 1.20−2.00(m, 16H), 0.87(t, J = 6.4 Hz, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 172.0, 80.6, 35.8, 31.7, 29.5, 29.3, 29.1, 27.8, 24.9, 22.6, 18.5, 14.1.

2.b. Preparation of Valerolactone 17 from Alcohol 16. By using the same procedure, a mixture of **16** (260 mg, 0.551 mmol), catalyst **9c** (50 mg, 0.0551 mmol), ligand **2c** (78 mg, 0.22mol), *N*-hydroxysuccinimide (380 mg, 3.31 mmol), sodium bicarbonate (93 mg, 1.1 mmol), tetra-*n*-butylammonium hexafluorophosphate (64 mg, 0.17 mmol) in DMF (1.4 mL, 0.4M) was placed in a preheated oil bath at 85 °C and stirred at that temperature for 26 h. The reaction mixture was cooled to room temperature, and DMF was removed under reduced pressure. The reaction mixture was purified directly by column chromatograhy (with deactivated silica gel, eluted with pet-ether/EtOAc 20:1) to give the dihydropyran (18 mg, 0.038, 7% yield). Further elution (with pet-ether/EtOAc 4:1) provided the starting material (2 mg, ∼1%) and the valerolactone **17** (175 mg, 0.358 mmol) as a clear oil (65% yield). $[\alpha]_D$ 70.7 (c 1.11, $CHCl_3$). R_f 0.55 (pet-ether/EtOAc 4:1).

IR (neat film): ν 3030, 2867, 1950, 1749, 1595, 1497, 1454, 1366, 1310, 1252, 1203 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz): δ 7.03−7.40 (m, 15H), 5.03(d, J = 11.0 Hz, 1H), 4.85(d, J = 10.5 Hz, 1H), 4.78(d, J = 11.0 Hz, 1H), 4.60(d, J = 12.1 Hz, 1H), 4.56(d, J = 12.1 Hz, 1H), 4.48(d, J = 10.5 Hz, 1H), 4.11(m, 1H), 3.60−3.82(m, 6H), 2.80-(ddd, J = 17.6, 9.5, 5.9 Hz, 1H), 2.61(m, 1H), 2.20(m, 1H), 1.96(m, 1H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 170.3, 138.1, 137.8, 137.7, 128.4, 128.1, 127.9, 127.8, 127.7, 94.0, 83.7, 81.3, 79.2, 77.2, 75.4, 73.5, 72.1, 68.6, 27.6, 24.3. HRMS: Calcd for $C_{30}H_{32}O_6$ (M^+): 488.2199. Found: 488.2193.

Acknowledgment. We thank the National Institutes of Health and the National Science Foundation for their generous support of our program. Mass spectra were provided by the Mass Spectrometry Facility at the University of California-San Francisco supported by NIH Division of Research Resources.

Supporting Information Available: Detailed descriptions of experimental procedures and spectral data for all new compounds (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

JA011840W

(33) The poor reactivity of tertiary bis-homopropargylic alcohols with stoichiometric amount of molybdenum complexes has been addressed: Weyershausen, B.; Nieger, M.; Dotz, K. H. *J. Organomet. Chem.* **2000,** *602*, 37.