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Chemoselective Cross Metathesis of Bishomoallylic Alcohols: Rapid Access to Fragment A of the Cryptophycins

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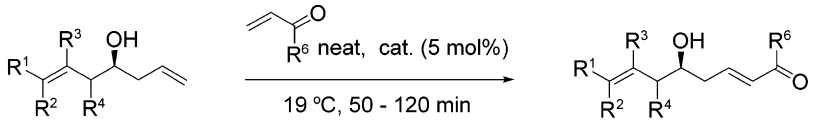
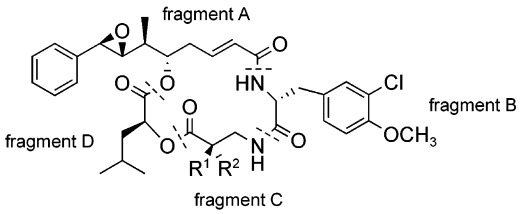
ABSTRACT



The racemic or enantioselective allylation of in situ formed *β,γ*-unsaturated aldehydes provides efficient access to bishomoallylic alcohols from readily available 2-vinyloxiranes. These products, when subjected to modified Grubbs cross metathesis conditions, afforded terminally homologated products in moderate to good yields with high *E* selectivity and without degradation of the enantiomeric excess. The compounds obtained through this two-step sequence yield fragments of an important and pharmacologically active family of cryptophycins.

The cryptophycins comprise a large family of natural, synthetic, and semisynthetic macro- and acyclic depsipeptides that have attracted a considerable amount of attention recently as a result of their exceptional pharmacological properties.[1] The low abundance of the cryptophycins combined with extraordinary clinical potential and their modular nature (Figure 1; fragment A−polyketide derived hydroxy acid; fragment B, C, D−amino acid based) has made them an ideal target for total synthesis and efforts to this end have been extensive.[2]



1 cryptophycin 1 (R^1 = Me, R^2 = H)
2 cryptophycin 52 (R^1 = R^2 = Me)
3 arenastatin A (R^1 = R^2 = H, deschloro in fragment B)

Figure 1. Various cryptophycin structures.

Recently we disclosed a high-yielding racemic protocol for the allylation or crotylation of various *β,γ*-unsaturated aldehydes, generated by the treatment of 2-vinyloxiranes with a Lewis acid (LA) (Figure 2).[3]

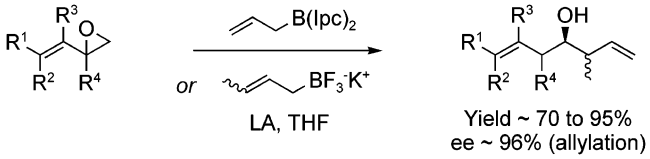


Figure 2. Access to bishomoallylic alcohols.

Extension of this methodology to an asymmetric version in the case of allylation afforded bishomoallylic alcohols as either antipode in excellent yields (Figure 2).[4] These products

(1) (a) Tius, M. A. *Tetrahedron* **2002**, *58*, 4343. (b) Shih, C.; Teicher, B. A. *Curr. Pharm. Des.* **2001**, *7*, 1259.
(2) For a complete list of references including reviews, total syntheses, fragment syntheses, and analogue preparation see Supporting Information.
(3) Lautens, M.; Ouellet, S. G.; Raeppel, S. *Angew. Chem., Int. Ed.* **2000**, *39*, 4079.

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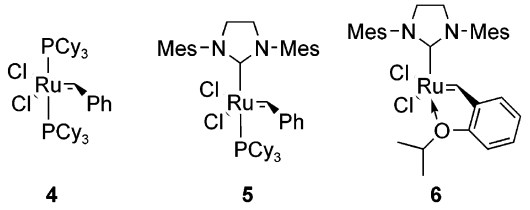
contain the basic core structure of fragment A (Figure 1) of the cryptophycins, and as such we feel this methodology is well suited to the rapid construction of a wide variety of structural analogues.

The advent of highly active and robust ruthenium metathesis catalysts (Figure 3, **4**,[5] **5**,[6] **6**[7]) has made cross

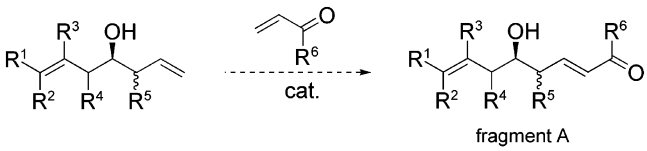


4 **5** **6**

Figure 3. Ruthenium-based metathesis catalysts.

metathesis (CM) an indispensable tool for the ready functionalization of simple olefinic substrates.[8] Of particular interest was the ability of second generation catalysts **5** and **6** to utilize acrylamides,[9] acrylic acid,[9] α,β-unsaturated aldehydes, ketones, or esters[10] as one component in the metathesis reaction. Homologation of the terminal olefin of a bishomoallylic alcohol (Scheme 1) would afford fragment

Scheme 1. Strategy for Selective Homologation



A type products in two steps from readily accessible 2-vinyloxiranes. We immediately recognized that competing ring-closing metathesis (RCM) could be a serious problem. Nevertheless we were optimistic that such a transformation might be possible because the terminal olefin should be both more electron-rich and sterically available. This report summarizes our efforts to this end.

Initial experiments were performed using Grubbs' first generation catalyst (**4**) but failed to afford any of the desired product under all of the conditions explored. We immediately shifted focus to the more active catalyst **5** and performed reactions under the conditions reported by Grubbs[9,10] with acrylic acid.

When the standard protecting groups were utilized at the carbinol center (Ac, TBDPS), only a trace amount of the desired α,β-unsaturated acids were isolated. However, when the secondary alcohol was left unprotected (**7**) we obtained significant amounts of the CM product (49%). The use of acrylic acid provided products that were inconvenient to purify. CM with *tert*-butyl acrylate gave a slightly lower yield (40%). Nevertheless, it was far easier to isolate the ester (**35**), and thus future optimization experiments were performed using this partner.

Chelation of oxygen functionalities to ruthenium during metathesis transformations is an important process.[7,11−13] The effect of a free hydroxyl group, be it positive or negative, is not altogether clear. There have been cases for allylic alcohols, even when protected as various ethers, where metathesis is effectively shut down,[12d,14] whereas in other cases it seems not to be important.[15] In light of these observations and our initial results (vide supra), we undertook a more exhaustive study of the effect of various protecting groups on the selective CM of the terminal olefin of a bishomoallylic alcohol.

A series of eight compounds (R = H, **7**; Ac, **8**; $C(O)CF_3$, **9**; Bn, **10**; MOM, **11**; TIPS, **12**; TBS, **13**; TBDPS, **14**) was prepared with varying coordination ability and steric requirements. Reaction with catalyst **5** provided information on the propensity of the starting material to undergo RCM as followed by ^{1}H NMR.[16] A portion of this NMR study is presented graphically in Figure 4.[17]

Immediately apparent was the dramatic difference in the rate of formation of styrene[16] for the free alcohol (**7**) relative to all of the protected derivatives (**8**−**14**). The overall rate of reaction was extremely rapid at catalyst loadings of 5 mol %, and no appreciable amount of starting material was observed after 3 min in all cases except for the free alcohol (**7**) and to a lesser extent with the MOM protecting group (**11**). The amount of styrene formed slowly

(4) Lautens, M.; Maddess, M. L.; Sauer, E. L. O.; Ouellet, S. G. *Org. Lett.* **2002**, *4*, 83.

(5) (a) Schwab, P.; France, M. B.; Ziller, J. W.; Grubbs, R. H. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 2039. (b) Schwab, P.; Grubbs, R. H.; Ziller, J. W. *J. Am. Chem. Soc.* **1996**, *188*, 100. (c) Belderrain, T. R.; Grubbs, R. H. *Organometallics* **1997**, *16*, 4001.

(6) (a) Scholl, S.; Ding, S.; Lee, C. W.; Grubbs, R. H. *Org. Lett.* **1999**, *1*, 953. (b) Sanford, M. S.; Love, J. A.; Grubbs, R. H. *J. Am. Chem. Soc.* **2001**, *123*, 6543.

(7) (a) Garber, S. B.; Kingsbury, J. S.; Gray, B. L.; Hovedya, A. H. *J. Am. Chem. Soc.* **2000**, *122*, 8168. (b) Gessler, S.; Randl, S.; Blechert, S. *Tetrahedron Lett.* **2000**, *41*, 9973.

(8) For a recent review, see: Connon, S. J.; Blechert, S. *Angew. Chem., Int. Ed.* **2003**, *42*, 1900.

(9) Choi, T.-L.; Chatterjee, A. K.; Grubbs, R. H. *Angew. Chem., Int. Ed.* **2001**, *40*, 1277.

(10) Chatterjee, A. K.; Morgan, J. P.; Scholl, M.; Grubbs, R. H. *J. Am. Chem. Soc.* **2000**, *122*, 3783.

(11) (a) Harrity, J. P. A.; La, D. S.; Wisser, M. S.; Hoveyda, A. H. *J. Am. Chem. Soc.* **1998**, *120*, 2343. (b) Kingsburry, J. S.; Harrity, J. P. A.; Bonitatebus, P. J.; Hoveyda, A. H. *J. Am. Chem. Soc.* **1999**, *121*, 791.

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(15) (a) Davoille, R. J.; Rutherford, D. T.; Christie, S. D. R. *Tetrahedron Lett.* **2000**, *41*, 1255. (b) Ovaa, H.; Codee, J. D. C.; Lastdrager, B.; Overkleeft, H. S.; Van der Marel, G. A.; Van Boom, J. H. *Tetrahedron Lett.* **1998**, *39*, 7987. (c) Schmidt, B.; Sattelkau, T. *Tetrahedron* **1997**, *53*, 12991. (d) Cossy, J.; BouzBouz, S.; Hoveyda, A. H. *J. Organomet. Chem.* **2001**, *624*, 327.

(16) The formation of styrene was used to measure the progress of RCM since it was the only consistently resolved signal for all the compounds studied.

(17) Full results are included in Supporting Information.

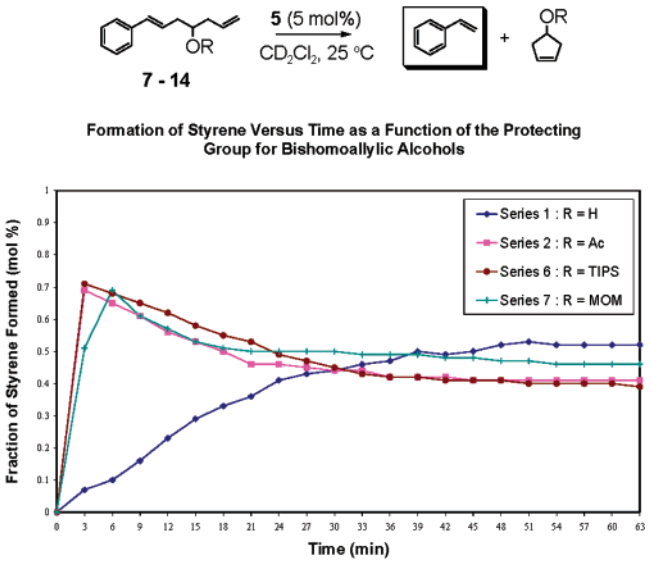


Figure 4. Formation of styrene as a function of alcohol protecting group.

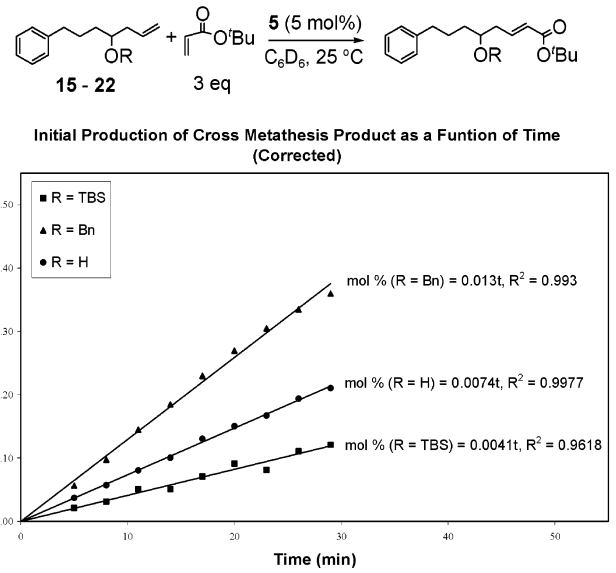


Figure 5. Formation of CM product as a function of time.

decreased with time as it is consumed in further metathesis reactions.

We were uncertain whether the rate of CM would be similarly affected by the protecting group R. Rather then study a system in which RCM and CM could occur simultaneously we decided to perform experiments in which the internal double bond was absent to isolate the process of interest. Once again a series of compounds was prepared (R = H **15**, Ac **16**, C(O)CF_3 **17**, Bn **18**, MOM **19**, TIPS **20**, TBS **21**, TBDPS **22**) and subjected to CM with *tert*-butyl acrylate and followed by ^{1}H NMR.[18] A portion of the NMR study[17] is presented graphically in Figure 5.

The results indicate that cross metathesis in this system is less sensitive to the nature of the protecting group compared to RCM especially with regard to the unprotected alcohol (**15**). The maximum rate was observed with the benzyl derivative (**18**), and the slowest reaction was with the TBS-protected alcohol (**21**); however, the difference between the two rates is only a factor of 4. Moreover the free alcohol is not the slowest to undergo reaction.

Overall there was no clear trend between coordination ability and rate, and it seems that a combination of factors is at play. These results along with the empirical observation that the unprotected bishomoallylic alcohol (**7**) consistently gave higher yields than protected derivatives led us to conclude that the free carbinol derivatives offered the best chance of obtaining the desired homologated products in good yields.

A solvent optimization study showed that concentration was the most important factor, and the best results were obtained when the reaction was neat in the acrylate metathesis partner (13 equiv).[19] Control experiments under the reaction conditions revealed that the product slowly degraded with time. Moreover both reaction time and temperature strongly influenced the amount of recovered product. Consequently these reactions were followed carefully by TLC at 19 °C, and when completed (typically 50 min), the reaction mixtures were loaded directly on a silica column and purified immediately. Although we were unable to observe an obvious trend with regard to the metathesis partner, empirically we found that methyl acrylate affords the highest yields of product.

In general the reaction conditions developed for the prototypical bishomoallylic alcohol (**7**) translated well to other substrates and in most cases the desired products were isolated in moderate to good yields.[20] Structural or electronic changes that deactivate the internal olefin improved the success of the reaction (Table 1, entries 4, 6, 7, and 9). Electron-rich substrates **25** and **28** (Table 1, entries 5 and 8) gave significantly reduced yields, and the simple alkyl substrate **33** failed to produce the desired product (Table 1, entry 13). Two other substrates (**30** and **32**) failed to give any of the homologated material. For **30** (Table 1, entry 10), the allylic methyl group inhibits the transformation to the desired CM product, perhaps by blocking coordination of the carbinol to ruthenium. For **32** (Table 1, entry 12) we believe chelation between the internal alkyne and free hydroxyl group sequestered the ruthenium catalyst, and the starting material was recovered unchanged (Table 1, entry 12).

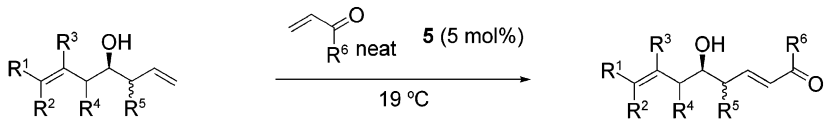
In general we typically observed only the (*E*)-α,*β*-unsaturated product to the limits of ^{1}H NMR detection. When

(18) Authentic samples of the CM products were prepared using conventional reaction conditions to facilitate the kinetic studies. These results are presented in Supporting Information.

(19) The yield improved steadily as the amount of coupling partner was increased up to a maximum at 13 equiv relative to the starting material. Higher loadings were not beneficial.

(20) Unless otherwise noted the material balance for the results in Table 1 consisted of small amounts of starting material, variable amounts of the RCM product (volatile), and small amounts of RCM/ring-opening metathesis CM products.

Table 1. Substrate Scope



	substrate							product			
entry	no.	R^1	R^2	R^3	R^4	R^5	R^6	time (min)	no.	yield (%)[a]	ee (%)[b]/note
1	**7**	Ph	H	H	H	H	OMe	50	**34**	73	
2	**7**	Ph	H	H	H	H	O^{t}Bu	50	**35**	64	
3	**23**[f]	Ph	H	H	Me	H	O^{t}Bu	50	**36**	60	dr ~ 1.2:1
4	**24**	$(CH_3)_2C{=}C(CH_2)_2$	Me	H	H	H	OMe	50	**37**	68	
5	**25**	*p*-(MeO)C_6H_4	H	H	H	H	OMe	50	**38**	43	94 (SM = 96)
6	**26**	*o*-$(NO_2)C_6H_4$	H	H	H	H	OMe	50	**39**	73	95 (SM = 96)
7	**27**	Ph	H	Me	H	H	O^{t}Bu	60	**40**	80[c]	*E*:*Z* = 22:1[d]
8	**28**	*o*-(MeO)C_6H_4	H	H	H	H	OMe	50	**41**	35	
9	**29**	Ph	Ph	H	H	H	OMe	50	**42**	84	
10	**30**	Ph	H	H	H	*syn*-Me	OMe	50	**43**	0	
11	**31**	R^1 to $R^3 = (CH_2)_4$, R^2 and R^4 = H				H	OMe	50	**44**	54 (72[e])	96 (SM = 96)
12	**32**	Ph	H	C≡CPh	H	H	OMe	120	**45**	nr	
13	**33**	$CH_3(CH_2)_4$	H	H	H	H	OMe	50	**46**	0	

[a] All reactions performed on a 0.5 to 1 mmol scale. Yields are isolated yields. [b] ee determined by chiral HPLC against racemic material; SM = starting material. [c] 10 mmol scale. [d] Separable. [e] Based on recovered starting material. [f] dr of SM ~1.2:1.

the reaction was performed on a larger scale (Table 1, entry 7), we were able to isolate both isomers and determined the ratio to be approximately 22:1 in favor of the *E* isomer. We suspect that this is also the case for the other substrates investigated. Finally we have shown that the enantiomeric excess is unchanged during the reaction conditions (Table 1, entries 5, 6, and 11).

In summary, the racemic or enantioselective allylation of in situ formed β,γ-unsaturated aldehydes provides efficient access to bishomoallylic alcohols from readily accessible 2-vinyloxiranes. These products, when subjected to modified Grubbs' cross metathesis conditions, afford terminally homologated products in moderate to good yields with high *E* selectivity and without degradation of enantiomeric excess. The compounds obtained through this two-step sequence afford fragments of an important and pharmacologically active family of natural products known collectively as the cryptophycins. In addition this methodology increases the utility of the original allylation chemistry, affording products wherein the two similar olefins are clearly differentiated.

Acknowledgment. We thank Merck Frosst Canada and NSERC (Canada) for an Industrial Research Chair, and the University of Toronto for financial support of this work. M.M. thanks NSERC (Canada) for financial support in the form of a postgraduate fellowship.

Supporting Information Available: Representative experimental procedures, complete results of NMR and optimization studies, and full characterization of all novel compounds, as well as related intermediates. This material is available free of charge via the Internet at http://pubs.acs.org.

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