



## Synthesis of Geometrically Defined Exocyclic Olefins

Youssef L. Bennani<sup>1</sup>, \*C.-K. Hwang<sup>2</sup>, Stacie S. Canan Koch, Kristin S. Marron,  
Laura J. Dardashti, Beth-Ann Badea and Alex M. Nadzan

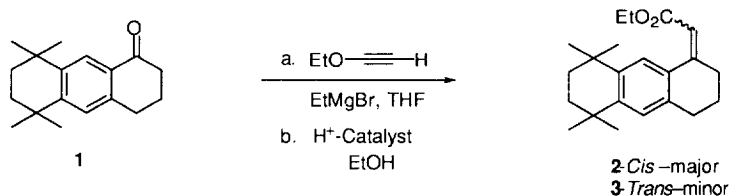
Department of Retinoid Chemistry Research, Ligand Pharmaceuticals Inc.,  
10255 Science Center Drive, San Diego, CA 92121, U.S.A.

**Abstract:** The treatment of bicyclic and tricyclic ketones with lithium ethynyl acetylide, followed by the addition of a catalytic amount of CSA or *p*-TSA, affords the corresponding exocyclic olefinic ester in good yields, and geometric ratios up to 13:1 favoring the *cis* olefin. This procedure represents an addition to the repertoire of olefination methods and can readily be extended to other cyclic and acyclic systems.

Copyright © 1996 Elsevier Science Ltd

The formation of olefins from carbonyl compounds is undoubtedly one of the cornerstones of synthetic organic chemistry.<sup>3</sup> Since the introduction of the Wittig reaction in the early fifties, many reagent-based variations have successfully emerged as powerful methods which enhance reagent reactivity and geometrical selectivity in olefin formation.<sup>4</sup> More recently, the asymmetric olefination of prochiral ketones also has been pioneered.<sup>5</sup> Despite such progress, the preparation of the less thermodynamically favored, but often desired *cis*-olefins remains a difficult process to achieve. In our research toward developing novel polyene retinoids for dermatological and cancer therapy,<sup>6</sup> we sought methods for the formation of constrained olefinic linkages that mimic various conformations of vitamin A carboxylic acid isomers, such as 9-*cis*- and all-*trans*-retinoic acids.<sup>7</sup> We wish to describe herein an improved method for achieving good to high levels of selectivity in the formation of *cis* exo-olefins for some carbocyclic and heterocyclic systems. In our attempts to convert  $\alpha$ -tetralone-like ketones such as **1** (Scheme 1) to the exocyclic *cis*-olefinic esters, several methods were investigated without initial success.<sup>8</sup> Whitehurst *et al.* have reported that the addition of ethylethynyl ether anion to  $\alpha$ -tetralone followed by treatment with carbon dioxide in ethanol affords the corresponding exocyclic olefinic esters as a ~2.4:1 *cis:trans* geometric mixture.<sup>9</sup>

Scheme 1



We have found that while this transformation is useful, the reaction is sluggish (>24 h for ~70% conversion), it requires continuous exposure to CO<sub>2</sub>, and give moderate geometric selectivities (Table 2). Accordingly, olefination of tricyclic ketone **1**, using the above conditions, produced the corresponding exocyclic olefinic esters **2** and **3** in 70% yield and a 4:1 *cis:trans* ratio. In order to increase the ratio in favor of the highly geometrically restricted *cis* isomer, we evaluated a variety of acid catalysts and temperatures to facilitate this transformation. We found that using catalytic amounts (~5 mol%) of bulky sulfonic or phosphonic acids generally improved the yields to above 85%, gave *cis:trans* selectivities in favor of the desired *cis* olefins of up to 13:1 (GC or <sup>1</sup>H NMR), and enhanced the reaction rate (between 30 min at -78°C to ~1 min at 25°C). The results, summarized in Table 1, indicate that a combination of low temperature (-78°C to 25°C) and the use of camphorsulfonic (CSA) or *p*-TSA afforded higher geometric selectivities. While there appears to be a general trend for higher selectivities with some sulfonic acids, the results obtained with 1-NSA and 2-NSA are not clear at the present time. It is noteworthy that using bulky trisubstituted ammonium halides such as dihydroquinidine hydrochloride (24 h. at RT), gave an olefinic ratio of 6:1 in favor of the *cis* isomer.

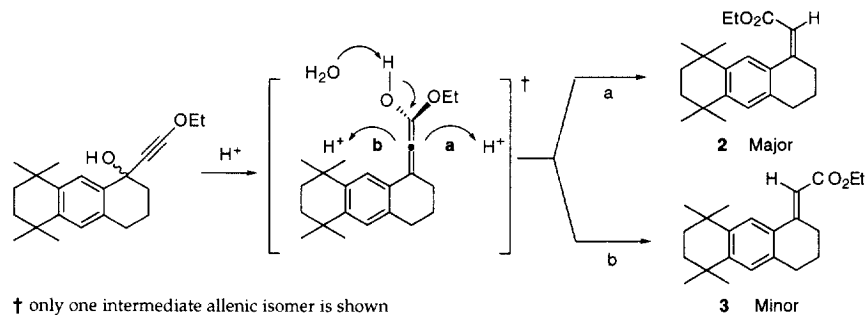
Table 1

Entry	Catalyst	Temp.	Cis: Trans	Entry	Catalyst	Temp.	Cis: Trans
<b>1</b>	HCl	25°C	1:1	<b>7</b>	CSA	-78 to 25°C	13:1
<b>2</b>	HCl	-78 to 25°C	2:1	<b>8</b>	1-NSA	-78 to 25°C	2:1
<b>3</b>	CO <sub>2</sub>	25°C	4:1	<b>9</b>	2-NSA	-78 to 25°C	3:1
<b>4</b>	<i>p</i> -TSA	0°C	6:1	<b>10</b>	DHQD.HCl	25°C	6:1
<b>5</b>	CSA	25°C	8:1	<b>11</b>	Binap-PA	-78 to 25°C	8:1
<b>6</b>	CSA	0°C	10:1	<b>12</b>	DP-PA	-78 to 25°C	11:1

Ratios were determined by GC or <sup>1</sup>H NMR (400 Mhz); *p*-TSA (*p*-Toluene Sulfonic Acid); CSA (Camphor Sulfonic Acid); NSA (Naphthyl Sulfonic Acid); DHQD (Dihydroquinidine); Binap-PA: Binaphthyl Phosphonic Acid; DP-PA (Diphenyl Phosphonic Acid).

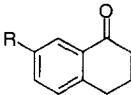
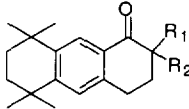
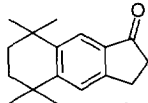
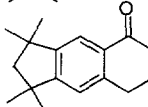
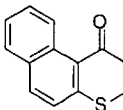
The observed dramatic increase in selectivity as a function of the size and acidity of the catalyst is indicative of a *regioselective kinetic protonation* of the allene intermediate as proposed earlier by Whitehurst and Tankard, Scheme 2.<sup>9</sup>

Scheme 2



Such intermediates, presumably formed through acid catalyzed dehydration-hydration, are then protonated from the less hindered side of the allene (path **a**) to give rise to the corresponding *cis* olefin. Formation of the thermodynamically favored *trans* olefin (path **b**) is minimized during the protonation step, due to strong steric interactions with both the pericyclic hydrogen and the geminal dimethyl group. Additionally, the results for the olefination of several bicyclic and tricyclic ketones, are depicted in Table 2.

Table 2

Entry	Ketone	% Olefin Yield <sup>a</sup>	<i>Cis: Trans</i> ratio <sup>b</sup>	
			Catalyst: CO <sub>2</sub>	CSA
				
1	(R=H)	73	2.4:1	5:1
2	(R=OMe)	80	4:1	4.6:1
				
3	R <sub>1</sub> =R <sub>2</sub> =H	75-90	4:1	13:1
4	R <sub>1</sub> =H; R <sub>2</sub> =Me	78	5:1	7:1
5	R <sub>1</sub> =R <sub>2</sub> =Me	71	3:1	5:1
6		78	2.5:1	6:1
7		73	2.5:1	5:1
8		61	1.4:1	2.3:1

a) Yield of isolated total olefins (mixture *Z:E*); b) Ratios determined by <sup>1</sup>H NMR or GC.

The olefination of  $\alpha$ -tetralone (Entry 1) under cat. CSA conditions gave a 5:1 *cis:trans* ratio as compared to 2.4:1 using CO<sub>2</sub>.<sup>9</sup> In the case of 7-methoxy-tetralone (Entry 2), no pronounced difference in selectivity was observed using CO<sub>2</sub> or CSA as catalysts. Several tricyclic substrates containing various substituents on the  $\alpha$ -methylene (Entry 3, 4, 5), or with an altered ring size pattern (Entry 6, 7), were evaluated under the above olefination conditions. In these cases, increased selectivity was observed and this is consistent with the proposed selective protonation approach favoring the formation of *cis* olefins.

Finally, olefination of naphthothiopyranone (Entry 8), a sterically challenging substrate for this reaction, gave a 2.3:1 ratio in favor of the *cis* olefin under our optimized CSA conditions. In all the tricyclic systems studied herein, excellent selectivities were obtained under acid catalysis. In summary, an improved method for the rapid preparation of geometrically defined *cis*- exocyclic olefins has been devised. This procedure represents an addition to the repertoire of olefination methods and can readily be extended to other cyclic and acyclic systems.<sup>10</sup> We are presently utilizing this methodology for the synthesis of novel retinoids which will be the subject of subsequent reports.

## References

1. Present address: Abbott Laboratories, 100 Abbott Park Rd, 4MG Abbott Park, IL 60064-3500, USA.
2. Present address: Amgen Inc., 3200 Walnut Street, Boulder Colorado 80301, USA.
3. a) Wittig, G.; Geissler, G. *Annalen*, **1953**, *44*, 580; b) Wittig, G.; Schöllkopf, U. *Chem. Ber.*, **1954**, *87*, 1318; c) Cadogan, J. I. G. in "Organophosphorus Reagents in Organic Synthesis", Academic Press, London, 1979; d) Maercker, A.; *Org. Synthesis* **1965**, *14*, 435; e) Kelly, S. E. in "Comprehensive Organic Synthesis, Addition to C-X Bonds", Part I, Vol. 4, Ed. S. L. Schreiber, Pergamon, Oxford, **1991**.
4. a) Horner, L.; Hoffmann, H.; Wippel, H. G. *Chem. Ber.* **1958**, *91*, 61; b) Wadsworth, W. S.; Emmons, W. D. *J. Am. Chem. Soc.* **1961**, *83*, 1733; c) Maryanoff, B.; Reitz, A. B. *Chem. Rev.* **1989**, *89*, 863; d) Hanessian, S.; Bannani, Y. L.; Leblanc, Y. *Heterocycles*, **1993**, *35*, 1411; e) Denmark, S. E.; Amburgey, J. *J. Am. Chem. Soc.* **1993**, *115*, 10386; f) Bartoli, G.; Marcontoni, E.; Sambri, L.; Tamburini, M. *Angew. Chem. Int. Ed. Engl.* **1995**, *34*, 2046 and references cited in all the above.
5. a) Hanessian, S.; Delorme, D.; Beaudoin, S.; Leblanc, Y. *J. Am. Chem. Soc.* **1984**, *106*, 5754; b) Hanessian, S.; Beaudoin, S. *Tetrahedron Lett.* **1992**, *33*, 7655 and 7659; c) Denmark, S. E.; Rivera, I.; *J. Org. Chem.* **1994**, *59*, 6887. d) Rein T.; Reiser O. *Acta Chemica Scandinavica* **1996**, *50*, 369.
6. a) Orfanos, C.E.; Ehlert, R.; Gollnick, H. "The Retinoids, A Review of Their Clinical Pharmacology and Therapeutic Use" *Drugs* **1987**, *34*, 459; b) Vokes, E. E.; Weichselbaum, R. R.; Lippman, S. M.; Hong, W. K. "Head and Neck Cancer" *N. Engl. J. Med.* **1993**, *328*, 184; c) Mangelsdorf, D. J.; Umesono, K.; Evans, R. M. "The Retinoids Receptors" in *The Retinoids*"; 2nd edition by M.B. Sporn, A.B. Roberts and D.S. Goodman, Raven Press, Ltd. New York, **1994**, 319.
7. a) Heyman, R. A.; Mangelsdorf, D. J.; Dyck, J. A.; Stein, R. B.; Eichelle, G.; Evans, R. M.; Thaller, C. *Cell* **1992**, *68*, 397; b) Dawson, M. I.; Okamura, W. H. "Chemistry and Biology of Synthetic Retinoids", CRC Press, **1990**; c) Sporn, M. B.; Roberts, A. B.; Goodman, D. S. in "The Retinoids: Biology, Chemistry and Medicine", 2d Ed. Raven Press, **1994**.
8. For example, the olefination of ketone **1** with the lithium anion of triethyl phosphonoacetate (*n*-BuLi, THF, reflux, 48 h), gave a mixture of *trans*-exo- $\alpha,\beta$ -unsaturated ester **3** and the endo ester (not shown) in 40% total yield. The reaction of the Li- or Na-anion derived from diethyl cyanomethyl phosphonate with ketone **1** produced the corresponding *trans*-exo-olefinic nitrile (*trans*:*cis* = 10:1). Conversion of **1** to the corresponding tricyclic triphenylphosphonium bromide (i. NaBH<sub>4</sub>, MeOH; ii. Ph<sub>3</sub>P-HBr) and reaction of the ylide with various aldehydes gave almost exclusively the *trans* exocyclic olefinic adducts. We have found that the reaction of ketone **1** with lithio-*t*-butyl trimethylsilyl acetate gave 40% of **2/3** esters in 8:1 (*Z*:*E*) ratio; (See a) Larson, G. L.; Betancourt de Perez, R. M. *J. Org. Chem.* **1985**, *50*, 5257; b) Kano, S.; Ebata, T.; Funaki, K.; Shibuya, S.; *Synthesis*, **1978**, 746.
9. a) Tankart, M. H.; Whitehurst, J. S. *J. Chem. Soc. Perkin I* **1973**, 615; b) Tankart, M. H.; Whitehurst, J. S. *Tetrahedron*, **1974**, *30*, 451.
10. For the addition of ethoxyacetylene anions or synthetic equivalents to carbonyl compounds: a) Stalick, W. M.; *Org. Proc. Int.*, **1988**, *20*, 275; b) Stalick, W. M.; Hazlett, R. N.; Morris, R. E., *Synthesis*, **1988**, 287; c) Tatlock, J. H. *J. Org. Chem.*; **1995**, *60*, 6221. For olefination of acyclic ketones and aldehydes using  $\alpha$ -chloroacetaldehyde diethyl acetal: d) Olah, G. A.; Wu, A-H.; Farooq O.; Prakash, S. G. K. *Synthesis*, **1988**, 537. For epoxide opening and *in situ* lactonization using diethylaluminium ethoxy acetylde: e) Danishefsky, S.; Tsai, M.; Kitahara, T. *J. Org. Chem.* **1977**, *42*, 394.

(Received in USA 26 August 1996; accepted 10 September 1996)