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Application of the Intramolecular Yamamoto Vinylogous Aldol Reaction to the Synthesis of Macrolides

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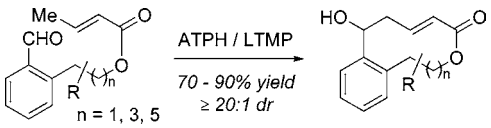
ABSTRACT



An intramolecular version of the Yamamoto vinylogous aldol reaction, a method that employs the bulky Lewis acid ATPH to control the site of aldolization, is described. This macrocyclization process is effective for the construction of 10-, 12-, and 14-membered macrolides. The yields are high (70–90%), and the reaction can proceed with excellent remote stereocontrol (dr ≥ 20:1) with chiral substrates.

The construction of medium and large membered rings has been an important and challenging problem in organic and natural products synthesis.[1] The intramolecular aldol reaction, although studied extensively for the assembly of small (five- to seven-membered) rings,[2] has only occasionally been employed for the synthesis of macrocycles.[3] Selective enolization, inter- vs intramolecular reactivity, and the possibility of enolate decomposition are issues that can complicate the macroaldolization process, and as such, intramolecular variations of the Mukaiyama and Reformatsky[4] reactions have constituted the majority of the macroaldolization examples known. Recently, Yamamoto described a method for performing vinylogous aldol reactions[5] with α,β-unsaturated carbonyl compounds and aldehydes in which both reactants are initially subjected to precomplexation with the bulky Lewis acid, aluminum tris(2,6-diphenylphenoxide) (ATPH), then treated with a bulky amide base, such as LDA or LTMP.[6] A simplified depiction of the ATPH−carbonyl complexes is provided in Scheme 1. Yamamoto has studied these structures in depth and has shown that the binding is flexible and subject to steric effects.[6d] The resulting ATPH-bound enolate then undergoes addition to the aldehyde at the terminal carbon of the enolate (Scheme 1). This positional selectivity is thought to be due to the bulk of the ATPH which blocks reaction at the proximal sites of the conjugated enolate.

The Yamamoto protocol is unusual in that both the aldehyde and the α,β-unsaturated carbonyl compound are

(1) For selected reviews on the synthesis of macrocycles, see: (a) Wessjohann, L. A.; Ruijter, E. *Top. Curr. Chem.* **2005**, *243*, 137. (b) Yet, L. *Chem. Rev.* **2000**, *100*, 2963. (c) Roxburgh, C. J. *Tetrahedron* **1995**, *51*, 9767. (d) Rousseau, G. *Tetrahedron* **1995**, *51*, 2777. (e) Meng, Q.; Hesse, M. *Top. Curr. Chem.* **1992**, *161*, 107. For a discussion of the role of strain in macrocyclic ring closure, see: (f) Galli, C.; Mandolini, L. *Eur. J. Org. Chem.* **2000**, *18*, 3117.

(2) Heathcock, C. H. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Heathcock, C. H., Eds.; Pergamon Press: Oxford, 1991; Vol. 2, p 133.

(3) For selected references relating to macroaldolization processes, see: (a) Tsuji, J.; Yamada, T.; Kaito, M.; Mandai, T. *Bull. Chem. Soc. Jpn.* **1980**, *53*, 1417. (b) Robin, J. P.; Gringore, O.; Brown, E. *Tetrahedron Lett.* **1980**, *21*, 2709. (c) Vögtle, F.; Mayenfels, P.; Luppertz, F. *Synthesis* **1984**, *7*, 580. (d) Kuroda, S.; Maeda, S.; Hirooka, S.; Ogisu, M.; Yamazaki, K.; Shimao, I.; Yasunami, M. *Tetrahedron Lett.* **1989**, *30*, 1557. (e) Hayward, C. M.; Yohannes, D.; Danishefsky, S. J. *J. Am. Chem. Soc.* **1993**, *115*, 9345. (f) Romero, M. A.; Franco, R. P.; Cruz-Almanza, R.; Padilla, F. *Tetrahedron Lett.* **1994**, *35*, 3255. (g) Takao, K.; Ochiai, H.; Yoshida, K.; Hashizuka, T.; Koshimura, H.; Tadano, K.; Ogawa, S. *J. Org. Chem.* **1995**, *60*, 8179. (h) Toshima, K.; Ohta, K.; Yanagawa, K.; Kano, T.; Nakata, M.; Kinoshita, M.; Matsumura, S. *J. Am. Chem. Soc.* **1995**, *117*, 10825. (i) Magnus, P.; Carter, R.; Davies, M.; Elliott, J.; Pitterna, T. *Tetrahedron* **1996**, *52*, 6283. (j) Meng, D.; Bertinato, P.; Balog, A.; Su, D.-S.; Kamenecka, T.; Sorensen, E. J.; Danishefsky, S. J. *J. Am. Chem. Soc.* **1997**, *119*, 10073. (k) Katoh, T.; Nagata, Y.; Yoshino, T.; Nakatani, S.; Terashima, S. *Tetrahedron* **1997**, *53*, 10253. (l) Caddick, S.; Delisser, V. M.; Doyle, V. E.; Khan, S.; Avent, A. G.; Vile, S. *Tetrahedron* **1999**, *55*, 2737. (m) Wei, C.-Q.; Zhao, G.; Jiang, X.-R.; Ding, Y. *Chem. Soc., Perkin Trans. 1* **1999**, 3531. (n) Rassu, G.; Auzzas, L.; Pinna, L.; Zambrano, V.; Zanardi, F.; Battistini, L.; Gaetani, E.; Curti, C.; Casiraghi, G. *J. Org. Chem.* **2003**, *68*, 5881.

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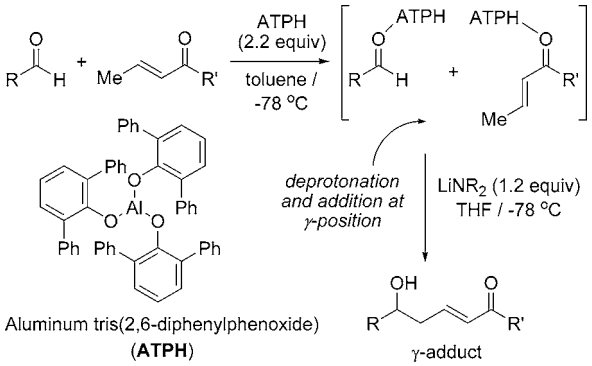
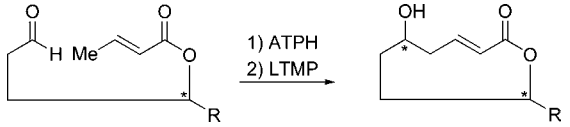
Scheme 1. Yamamoto Vinylogous Aldol Reaction



present prior to the addition of the base. As such, we felt that this method could be applied to the macroaldolization of crotonate esters (Scheme 2),[7] and we describe herein our

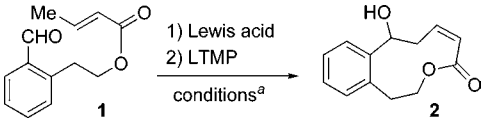
Scheme 2. Intramolecular Yamamoto Vinylogous Aldol Reaction



initial results which establish this as an effective method for macrocyclic ring synthesis. Furthermore, we show that these cyclizations can proceed with high levels of remote asymmetric induction.

In our initial studies, we examined the cyclization of compound **1** (Table 1). Yamamoto has described different reaction conditions for various substrate combinations,[6] and in our first cyclization attempts, we used a slight modification

Table 1. Optimization Studies



entry	Lewis acid	LTMP equiv	temp	% yield[b]
1	ATPH	1.1	−25	25
2	none	1.1	−25	0
3	Me_3Al	1.1	−25	0
4	ATPH	1.1	−78	34
5	ATPH	1.1	0	6
6	ATPH	2.0	−78	44
7	ATPH	2.0	−25	50
8	ATPH	2.0	−48	62
9	ATPH	2.0	−48	70[c]

[a] LTMP was slowly added to a solution of **1** precomplexed with the specified Lewis acid (2.2 equiv) at the specified temperature (°C). All reactions were performed at a 0.01 M final substrate concentration in 10:1 toluene/THF. [b] Isolated yield after purification. [c] A solution of the **1**−ATPH complex was slowly added to a solution of LTMP.[11]

of one of these wherein a solution of LTMP (1.1 equiv) in THF was added to a solution of **1** and ATPH (2.2 equiv) in toluene at −25 °C.[6b] We were pleased to find that these conditions provide the desired macrolide (**2**) albeit in only 25% yield (entry 1). The stereochemistry of the alkene of **2** was assigned as *Z* on the basis of the coupling constant between the alkenyl protons (11.2 Hz).[8] In the absence of ATPH, or in the presence of the precursor to ATPH, Me_3Al,[9] none of the desired product was observed (entries 2 and 3).[10] A brief solvent survey was conducted wherein we studied cyclizations in dichloromethane, toluene, and THF and found that these solvents provided only trace amounts of product (data not shown).[10] At lower temperature (−78 °C), a slight improvement in yield was observed (34%, entry 4); however, at higher temperatures (0 °C), the yield decreased significantly (6%, entry 5).[10] The best results were obtained when the amount of LTMP used was increased from 1.1 to 2.0 equiv (entries 6−9), and under these conditions at −48 °C, a 62% yield was observed (entry 8). Finally, it was found that reversing the order of addition, such that a solution of **1** and ATPH (2.2 equiv) in toluene was slowly added to a cooled (−48 °C) solution of LTMP (2.0 equiv) in THF/toluene, cleanly provides **2** in 70% yield (entry 9).[11]

Using these optimized conditions,[11] we examined the cyclizations shown in Table 2. We wished to study the effects of ring size and whether or not remote asymmetric induction could be observed in these reactions.

Entries 1−3 describe cyclizations which produce 10-membered rings, and we were pleased to find that these reactions proceed in high yields (77−82%) and with excellent

(4) For Mukaiyama and Reformatsky macrocyclizations, see: (a) Maruoka, K.; Hashimoto, S.; Kitagawa, Y.; Yamamoto, H.; Nozaki, H. *J. Am. Chem. Soc.* **1977**, *99*, 7705. (b) Smith, A. B.; Gauciaro, M. A.; Schow, S. R.; Wovkulich, P. M.; Toder, B. H.; Hall, T. W. *J. Am. Chem. Soc.* **1981**, *103*, 219. (c) Tabuchi, T.; Kawamura, K.; Inanaga, J.; Yamaguchi, M. *Tetrahedron Lett.* **1986**, *33*, 3889. (d) Vedejs, E.; Ahmad, S. *Tetrahedron Lett.* **1988**, *29*, 2291. (e) Mukaiyama, T.; Shiina, I.; Iwadare, H.; Saitoh, M.; Nishimura, T.; Ohkawa, N.; Sakoh, H.; Nishimura, K.; Tani, Y.; Hasegawa, M.; Yamada, K.; Saitoh, K. *Chem.−Eur. J.* **1999**, *5*, 121. (f) Inoue, M.; Sasaki, M.; Tachibana, K. *J. Org. Chem.* **1999**, *64*, 9416. (g) Hachiya, I.; Kobayashi, N.; Kijima, H.; Pudhom, K.; Mukaiyama, T. *Chem. Lett.* **2000**, *8*, 932. (h) Hong, Z.; Xu, X. *Tetrahedron Lett.* **2003**, *44*, 489. (i) Kigoshi, H.; Kita, M.; Ogawa, S.; Itoh, M.; Uemura, D. *Org. Lett.* **2003**, *5*, 957. (j) Nagamitsu, T.; Takano, D.; Fukuda, T.; Otoguro, K.; Kuwajima, I.; Harigaya, Y.; Omura, S. *Org. Lett.* **2004**, *6*, 1865.

(5) For reviews on the vinylogous aldol reaction, see: (a) Casiraghi, G.; Zanardi, F.; Appendino, G.; Rassu, G. *Chem. Rev.* **2000**, *100*, 1929. (b) Denmark, S. E.; Heemstra, J. R.; Beutner, G. L. *Angew. Chem., Int. Ed.* **2005**, *44*, 4682.

(6) (a) Saito, S.; Shiozawa, M.; Ito, M.; Yamamoto, H. *J. Am. Chem. Soc.* **1998**, *120*, 813. (b) Saito, S.; Shiozawa, M.; Yamamoto, H. *Angew. Chem., Int. Ed.* **1999**, *38*, 1769. (c) Saito, S.; Shiozawa, M.; Nagahara, T.; Nakadai, M.; Yamamoto, H. *J. Am. Chem. Soc.* **2000**, *122*, 7847. (d) Saito, S.; Nagahara, T.; Shiozawa, M.; Nakadai, M.; Yamamoto, H. *J. Am. Chem. Soc.* **2003**, *125*, 6200. (e) For an asymmetric variation, see: Takikawa, H.; Ishihara, K.; Saito, S.; Yamamoto, H. *Synlett* **2004**, 732.

(7) For an example of an intramolecular vinylogous aldol reaction, see: Takao, K.-i.; Hiroshi, O.; Yoshida, K.-i.; Hashizuka, T.; Koshimura, H.; Tadano, K.-i.; Ogawa, S. *J. Org. Chem.* **1995**, *60*, 8179.

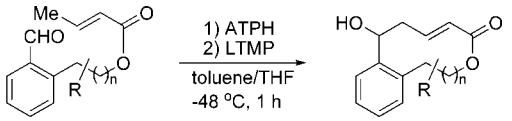
(8) See the Supporting Information for details.

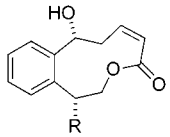
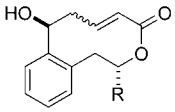
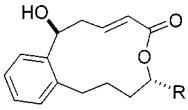
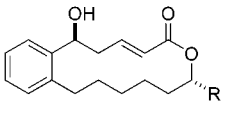
(9) ATPH is prepared by the treatment of Me_3Al (1 equiv) with 2,6-diphenylphenol (3 equiv). See Supporting Information or ref 6a for details.

(10) Varying amounts of starting material and unidentified side products were observed in these reactions.

(11) For details, see the general cyclization procedure in the Supporting Information.

Table 2. Scope of the Intramolecular Vinylogous Aldol Reaction

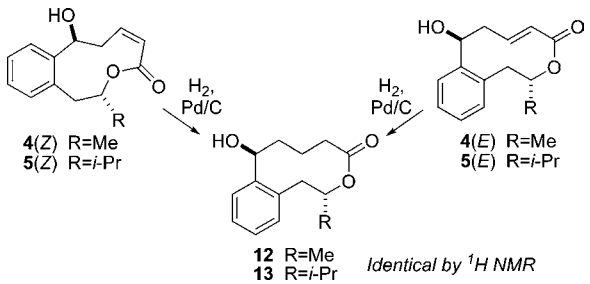


entry	product	R	yield[a]	Z/E[b]	dr[c]
1		Me (**3**)	80%	*Z*	> 25:1[e]
2		Me (**4**)	77%	3/1	> 25:1[e]
3		*i*-Pr (**5**)	82%	1/13	> 25:1[e]
4		H (**6**)	81%[d]	*E*	—
5		Me (**7**)	84%	*E*	> 25:1[e]
6		*i*-Pr (**8**)	83%	*E*	> 25:1[e]
7		H (**9**)	90%	*E*	—
8		Me (**10**)	89%	*E*	20:1
9		*i*-Pr (**11**)	88%	*E*	23:1

[a] Isolated yield after purification. [b] Ratio of alkene stereoisomers produced. [c] Diastereomeric ratios determined by ^{1}H NMR. [d] The macrodiolide was also isolated in 7% yield. [e] A single isomer was observed by ^{1}H NMR.

levels of asymmetric induction (>25:1 dr). In the case of entry 1, the *Z*-alkene was produced and no diastereomeric products were detected by ^{1}H NMR. Entries 2 and 3 show an interesting trend wherein an increase in the steric bulk of the substituent on the ring provides increasing amounts of the *E*-alkene[8] (compare Table 1, R = H, exclusively *Z*, with Table 2, entry 2, R = Me, 3:1 *Z*/*E*, and Table 2, entry 3, R = *i*-Pr, 1:13 *Z*/*E*). In the case of entries 2 and 3, hydrogenation of the isomeric products provides the same compound, thereby indicating that the compounds have the same relative stereochemistry between the two tetrahedral stereocenters and differ only by the alkene geometry (Scheme 3).

Scheme 3



Entries 4−6 in Table 2 describe cyclizations which produce 12-membered macrolides, and these reactions also proceed in high yields (81−84%) and produce the *E*-isomers exclusively. We were pleased to again observe excellent levels of remote asymmetric induction (≥25:1 dr) and were unable to detect any isomeric products in these reactions by ^{1}H NMR. Interestingly, these products display fluxional behavior at the intermediate exchange rate on the NMR time scale with broad nondescript signals at room temperature. When heated to 59 °C, the spectra sharpen as described in the Supporting Information.

Entries 7−9 in Table 2 describe cyclizations which form 14-membered rings, and these reactions proceed in the highest yields of all those that we studied (88−90%). Again, *E*-alkenes are produced exclusively, and the reactions proceed with high levels of remote asymmetric induction (entry 8, R = Me, 20:1, entry 9, R = *i*-Pr, 23:1). The diastereomeric ratio was determined by ^{1}H NMR integration of the alkenyl protons. Furthermore, hydrogenation of the alkene of compounds **10** and **11** provides products in which the isomeric ratio is maintained, thereby indicating that **10** and **11** are isomeric at the tetrahedral stereocenters and not at the alkene.

The relative stereochemistry for lactone **3** was determined by X-ray crystallography to be syn as drawn in Table 2, whereas that of lactones **4** and **7** was determined to be anti as drawn in Table 2 and as shown in Figure 1.[12,13]

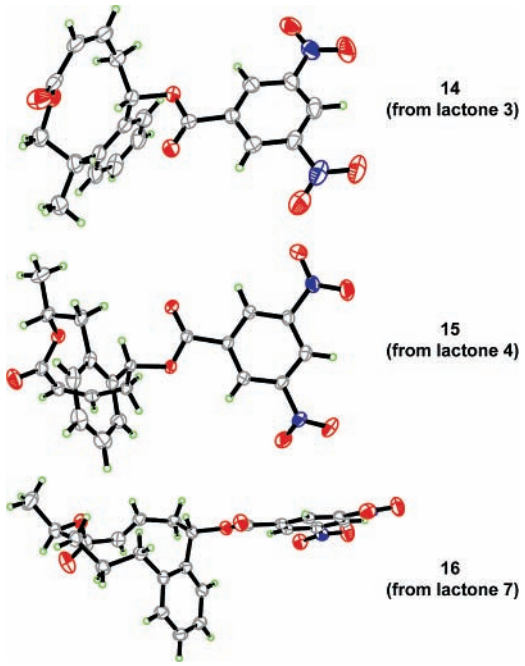
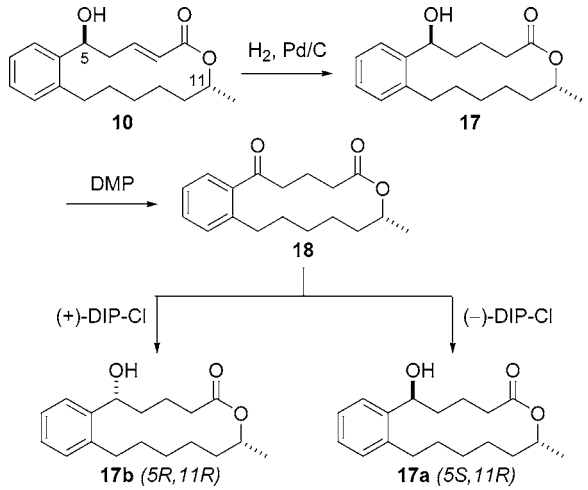


Figure 1. X-ray crystal structures of the 3,5-dinitrobenzoate derivatives of lactones **3**, **4**, and **7**.

The relative stereochemistry of lactone **10** was determined to be anti by chemical correlation as shown in Scheme 4.[14] Compound **10** was synthesized with control of the absolute

(12) Crystallographic data for the 3,5-dinitrobenzoates **14** and **15** can be found in the Supporting Information. The stereochemistry of compound **5** was assigned by analogy.

Scheme 4



stereochemistry at C-11 (*R*), then hydrogenated (Pd/C) to provide **17**. Oxidation of **17** (Dess−Martin periodinane)[15] to ketone **18** was followed by asymmetric reduction with (−)-DIP−Cl[16] to provide **17a** (5*S*,11*R*) and (+)-DIP−Cl to provide **17b** (5*R*,11*R*). Alcohol **17** derived from compound **10** has spectral properties identical to those of **17a** (5*S*,11*R*) and different spectral data from those of **17b** (5*R*,11*R*), thereby establishing that lactone **10** has the *S* configuration at C5 and an anti relationship between the two tetrahedral stereocenters in the macrolide, as drawn in Table 2 and Scheme 4.

In conclusion, we have described an intramolecular variation of the Yamamoto vinylogous aldol reaction for the construction of 10- to 14-membered macrolides in good yields (up to 90%) and excellent remote diastereoselection (≥20:1 dr). Studies aimed at understanding the stereocontrol element in these cyclizations, expanding the scope of this method, and applying it to the synthesis of natural products are in progress.

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Supporting Information Available: Spectral characterization and experimental procedures for the synthesis of compounds **1**−**18** and a general cyclization procedure. This material is available free of charge via the Internet at http://pubs.acs.org.

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(13) Crystallographic data for the 3,5-dinitrobenzoate **16** can be found in the Supporting Information. The stereochemistry of compound **8** was assigned by analogy.

(14) The stereochemistry of compound **11** was assigned by analogy.

(15) Dess, D. B.; Martin, J. C. *J. Am. Chem. Soc.* **1991**, *113*, 7277.

(16) Chandrasekharan, J.; Ramachandran, P. V.; Brown, H. C. *J. Org. Chem.* **1985**, *50*, 5446.