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Stereoselective Synthesis of (*E*)-2-En-4-ynoic Acids with Ynolates: Catalytic Conversion to Tetronic Acids and 2-Pyrones

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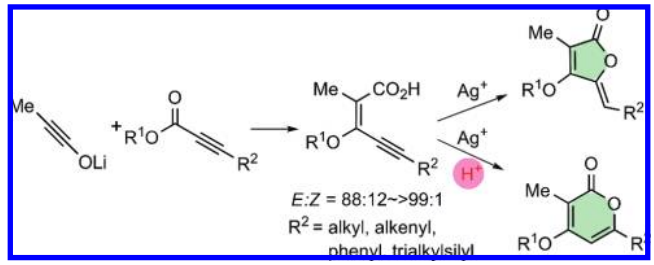
ABSTRACT



A highly torquoselective olefination of alkynoates to provide functionalized tetrasubstituted olefins, (*E*)-2-en-4-ynoic acids, is described. Addition of Brønsted acids dramatically switched the mode of the Ag(I)-catalyzed cyclization of the resulting enyne carboxylic acids to give either tetronic acids or 2-pyrones.

Since tetronic acid is frequently found in biological natural products as an active site unit,[1,2] it was thought that the 5-*exo* cyclization of (*E*)-2-en-4-ynoic acids **1** could afford the tetronic acid derivatives **2**[3−6] and that the 6-*endo* cyclization of **1** would furnish 2-pyrones **3**,[7] which could be good substrates for Diels−Alder reactions (Figure 1).[8] A regioselective cyclization of **1** therefore would be a useful method for the preparation of **2** and **3**. However, as of yet there is no efficient method available for the stereoselective preparation of β-alkoxy enyne carboxylic acids **1**.

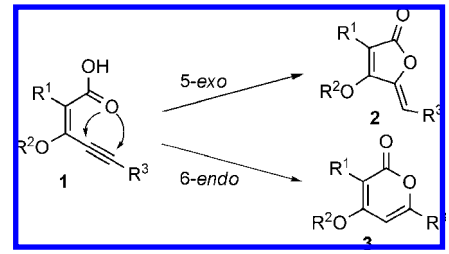


Figure 1. Tetronic acid derivatives (5-*exo*) vs pyrones (6-*endo*) cyclization.

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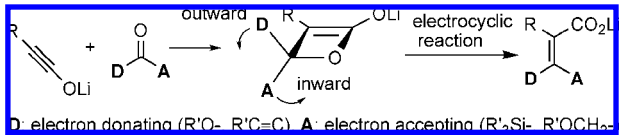
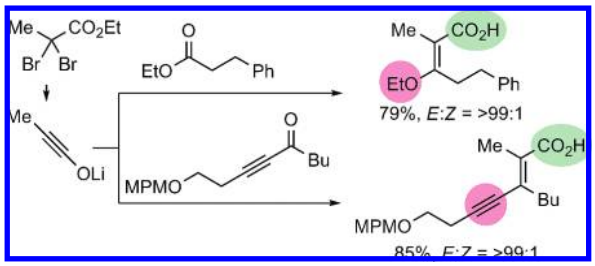
We have developed a torquoselective olefination for carbonyl compounds with ynolates to give multisubstituted alkenes with high stereoselectivities[9] in which the β-lactone enolate intermediates are ring-opened with high torquoselectivity.[10] In this method, electron donating substituents rotate outward whereas electron-accepting substituents rotate inward to afford the stereodefined products (Scheme 1). During the course of this

Scheme 1. Torquoselective Olefination



study, esters[11] and alkynyl alkyl ketones[12] were found to be olefinated with excellent *E* selectivities, where alkoxy and alkynyl groups act as strong electron donating groups (Scheme 2). Consequently, the torquoselectivity of alkynoic acid esters,

Scheme 2. Olefination of the Alkynyl Ketone and Ester



or alkynoates, is of interest to determine their relative outward rotating abilities.[13]

Herein, we describe the highly *E*-selective olefination of alkynoates with ynolates to provide tetrasubstituted alkenes and their Ag(I)-catalyzed cyclization to give either tetronic acids or pyrones under appropriate conditions.

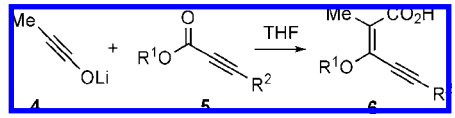
The ynolate **4**, prepared from the reaction of ethyl 2,2-dibromopropionate with *t*-BuLi,[14] reacted with isobutyl 3-(*tert*-butyldimethylsilyl)propiolate (**5a**) to afford the tetrasubstituted olefin **6a** in a *E*/*Z* ratio of 98.5:1.5 (Table 1, entry 1). Encouraged by this result, we decided to examine the olefination of several kinds of alkynoates as substrates, as shown in Table 1. The esters with a silyl or an alkoxymethyl substituent on the terminal ethynyl group afforded olefins with excellent selectivity (entries 2, 3, and 4), while the 2-hexynoate and 5-phenylpent-3-en-2-ynoate provided *E*-olefins along with a small amount of the minor *Z*-isomers (entries 5 and 6). However the 3-phenyl-2-propynoate afforded the olefin with high *E* selectivity (entry 7). In these electrocyclic reactions, the alkoxy group prefers outward rather than inward rotation compared to the alkynyl group, and the substituent on the terminal position of the ethynyl group has only a slight effect on the torquoselectivity.

The Ag_2CO_3-catalyzed cyclization[4c,e] of **6g** was carried out in various solvents to examine the selective synthesis of 5-*exo* or 6-*endo* products (Table 2, entries 1−4). In DMF, 5-*exo* cyclization proceeded selectively to give the tetronic acid derivative **7g** (entry 1). The reaction in THF also favored 5-*exo* cyclization, albeit with lower selectively (entry 2). In benzene and dichloromethane, the 6-*endo* cyclized product **8g** was generated with poor selectivity (entries 3 and 4).

We next examined the effect of the counterions of the silver salts in DMF (Table 2, entries 5−8). Ag_2O allowed an efficient 5-*exo* cyclization (entry 5), and AgOAc and $AgClO_4$ led to poor selectivity (entries 6 and 7). In contrast, $AgSbF_6$ catalyzed the reaction to afford the 6-*exo* cyclized product **8g** preferentially (entry 8).

Since Ag_2CO_3 and Ag_2O are oxidizing agents of oxygen functional groups,[15] they could be used to activate the carboxyl group to form a metal carboxylate, which would stereoelectronically favor a 5-*exo* cyclization, along with slight activation of the alkyne by the Ag(I) catalysts. On the other hand, $AgSbF_6$ is known for forming π complexes with

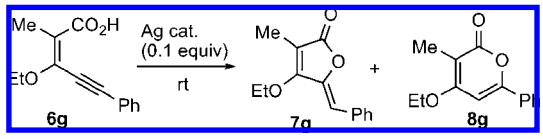
Table 1. Olefination of Alkynoates with Ynolates



entry	R^1	R^2	**5**	conditions	yield (%)	*E*:*Z*[a]
1	*i*-Bu	TBS	**5a**	−78 °C to rt, 1.5 h	63 (**6a**)	98.5:1.5
2	*i*-Bu	TMS[b]	**5b**	−78 to −20 °C, 1 h	51 (**6b**)	>99:1
3	*i*-Bu	$MPMOCH_2$	**5c**	−40 °C to rt, 4 h	71 (**6c**)	>99:1
4	Et	TES	**5d**	−78 to −20 °C, 2 h	41 (**6d**)	>99:1
5	Et	Bu	**5e**	−78 °C to rt, 1 h	48 (**6e**)	88:12
6	Et	*trans*-PhCH=CH	**5f**	−78 °C to rt, 1 h	62 (**6f**)	89:11
7	Et	Ph	**5g**	−40 °C to rt, 2 h	49 (**6g**)	97:3

[a] Stereochemistry was determined by NOE experiments of the products or their corresponding derivatives. See Supporting Information. [b] TMS group was converted to H by addition of water after olefination.

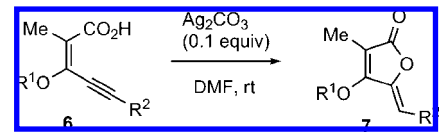
Table 2. Ag(I)-Catalyzed Cyclization of (*E*)-2-En-4-ynoic Acids



entry	Ag cat.	solvent	time (h)	yield (%)	**7g:8g**[a]
1	Ag_2CO_3	DMF	1	90	>95:5
2	Ag_2CO_3	THF	5	80	63:37
3	Ag_2CO_3	benzene	12	84	42:58
4	Ag_2CO_3	CH_2Cl_2	5	80	40:60
5	Ag_2O	DMF	1	68	93:7
6	AgOAc	DMF	1	71	86:14
7	$AgClO_4$	DMF	1	87	63:37
8	$AgSbF_6$	DMF	1	89	9:91

[a] Ratios were determined by ^{1}H NMR.

Table 3. Ag(I)-Catalyzed 5-*exo* Cyclization Leading to Tetronic Acids



entry	R^1	R^2	**6**	time (h)	yield (%)
1	*i*-Bu	TBS	**6a**	1	93 (**7a**)
2	*i*-Bu	H	**6b**	1	57 (**7b**)
3	*i*-Bu	$MPMOCH_2$	**6c**	1.5	79 (**7c**)
4	Et	TES	**6d**	1	78 (**7d**)
5	Et	Bu	**6e**	1.5	86[a] (**7e** + **8e**)
6	Et	*trans*-PhCH=CH	**6f**	1.5	74 (**7f**)
7	Et	Ph	**6g**	1	90 (**7g**)

[a] The product was a 4:1 mixture of **7e** and **8e**.

alkynes.[16,17] The polarized alkyne was attacked at the δ-position of the carboxylate resulting in 6-*endo* cyclization. AgOAc and $AgClO_4$ can exhibit hybrid activation[18] for both oxygen and alkyne which may account for the poor selectivity.[19]

On the basis of these results, we carried out the cyclization of enyne carboxylic acids (**6a**−**g**) bearing various kinds of substituents to explore the generality of this method, as shown in Table 3. Most of the substrates afforded the 5-*exo* cyclized products **7** without the 6-*endo* cyclized products (entries 1−4, 6, and 7). When the R^2 group was Bu, a 4:1 mixture of **7e** and **8e** was obtained (entry 5).

However, when the Ag(I) catalyzed cyclization of **6** was performed in the presence of Brønsted acids, the pyrones **8** resulted. Although the conversion of **6e** to **8e** with a combination of Ag_2CO_3 and AcOH in DMF showed no selectivity (50:50) (Table 4, entry 1), the 6-*endo* products were produced exclusively in CH_2Cl_2 (entries 2 and 4). A slight excess of AcOH compared to the Ag(I) catalyst was required to achieve selective 6-*endo* cyclization. The reaction with AcOH in the absence of Ag_2CO_3 did not go to completion (entries 3 and 5). When the R^2 group was $MPMOCH_2$, a 3:1 mixture of **8c** and **7c** was obtained (entry 6). There was no difference in the selectivity when CF_3CO_2Ag was used in place of Ag_2CO_3 (entry 7). In contrast, CF_3CO_2H (TFA) worked efficiently as an acid to afford the 6-*endo* product (entry 8). However, when the reaction rate was sluggish, the acidity of TFA was so strong that the β-alkoxy-α,β-unsaturated carboxylic acid **3** was isomerized to (*Z*)-**6c** (entry 9). On the other hand, the silyl-substituted alkynes gave exclusively the 5-*exo* products, probably due to a stereoelectronic effect (entries 10 and 11). These results suggest that Brønsted acids and nonpolar solvent are effective in promoting 6-*endo* cyclization and that Ag(I) catalysts increase the reaction rate by strong complexation with the alkyne.

We sought to understand the 6-*endo* selective cyclization with Brønsted acids through DFT-B3LYP/6-31+G* calculations[20] using Gaussian 03 software. Uchiyama et al. explained the 5-*exo* vs 6-*endo* cyclization based on the electronic bias of the groups on both carbons of the triple bond.[4f] We also observed a similar electronic bias on the carbons of the triple bond as shown in Figure 2, that is, the more electrophilic carbon atom at the δ-position induced the 6-*endo* cyclization.

To demonstrate the synthetic utility of the cyclization, an elongation of the carbon skeleton of the terminal alkene of the

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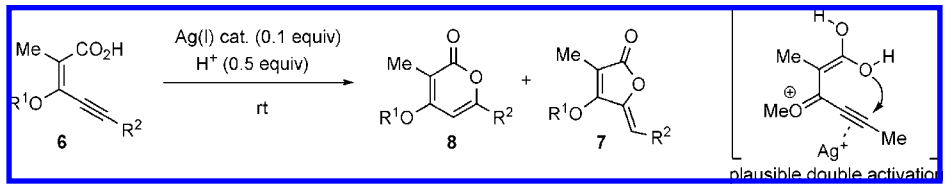
Table 4. Ag(I)-Catalyzed 6-*endo* Cyclization for Pyrones



entry	R^1	R^2	**6**	Ag cat.	H^+	solvent	time (h)	yield (%)	**8**:**7**
1	Et	Bu	**6e**	Ag_2CO_3	AcOH	DMF	1.5	64 (**8e**)	50:50
2	Et	Bu	**6e**	Ag_2CO_3	AcOH	CH_2Cl_2	9	73 (**8e**)	>99:1
3	Et	Bu	**6e**	none	AcOH	CH_2Cl_2	9	49[a] (**8e**)	>99:1
4	Et	Ph	**6g**	Ag_2CO_3	AcOH	CH_2Cl_2	9	64 (**8g**)	>99:1
5	Et	Ph	**6g**	none	AcOH	CH_2Cl_2	9	no reaction	
6	*i*-Bu	$MPMOCH_2$	**6c**	Ag_2CO_3	AcOH	CH_2Cl_2	14	70 (**8c**)	75:25
7	*i*-Bu	$MPMOCH_2$	**6c**	$Ag(OCOCF_3)$	AcOH	CH_2Cl_2	9	45 (**8c**)	78:22
8	*i*-Bu	$MPMOCH_2$	**6c**	Ag_2CO_3	TFA	CH_2Cl_2	1.5	64 (**8c**)	93:7
9	*i*-Bu	$MPMOCH_2$	**6c**	none	TFA	CH_2Cl_2	1.5	43[b] (**8c**)	>99:1
10	*i*-Bu	TBS	**6a**	Ag_2CO_3	AcOH	CH_2Cl_2	17	97[c] (**7a**)	<1:99
11	Et	TES	**6d**	Ag_2CO_3	AcOH	CH_2Cl_2	17	62[c] (**7d**)	<1:99

[a] Reaction was not completed. [b] Product was a 1:2 mixture of **8c** and the *Z*-isomer of **6c**. [c] Product was a diastereomeric mixture of the tetronic acid derivatives **7**.

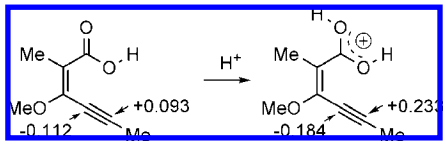
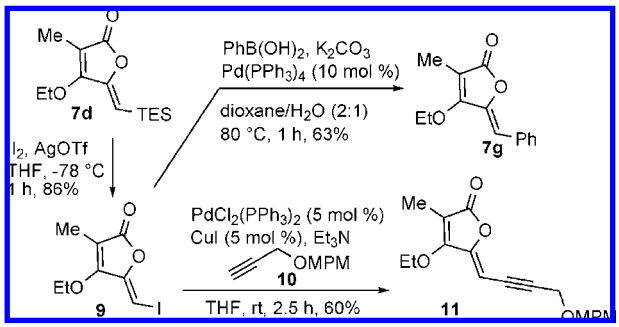


Figure 2. Natural population analysis (B3LYP/6-31+G*).

tetronic acids was attempted, since this kind of tetronic acid derivative is often seen in bioactive natural products (Scheme 3). The TES-substituted tetronic acid derivative **7d** was converted to vinyl iodide **9** by treatment with iodine in the presence of AgOTf.[21] The Suzuki−Miyaura coupling between **9** and phenylboronic acid was conducted to provide **7g** in 60% yield.[22] The Sonogashira coupling between **9** and the terminal alkyne **10** also proceeded to afford **11** in 63% yield.[23]

Scheme 3. Elongation of the Carbon Skeleton of the Tetronic Acids



In conclusion, we have shown that a highly torquoselective olefination of alkynoates provides functionalized tetrasubstituted olefins. The mode of the cyclization of the enyne carboxylic acids was dramatically altered by addition of Brønsted acids resulting in the selective synthesis of tetronic acid derivatives and pyrones. Further studies will be carried out to apply this methodology to the synthesis of bioactive natural products.

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Supporting Information Available: General procedures, characterization data of new compounds, ^1H and ^{13}C NMR spectra of new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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