

1 Lipase-mediated epoxidation utilizing urea–hydrogen peroxide in ethyl acetate†

5 Emanuel Ankudey,^a Horacio F. Olivo^{*b} and Tonya L. Peoples^a

Received 7th April 2006, Accepted 18th July 2006

First published as an Advance Article on the web

DOI: 10.1039/b604984b

10 A green method for alkene epoxidation based on the chemo-enzymatic perhydrolysis of carboxylic acids and esters has been optimized using Novozyme 435, the immobilized form of *Candida antarctica* lipase B, and the complex urea–hydrogen peroxide (UHP). UHP, an anhydrous form of hydrogen peroxide, has the potential of releasing hydrogen peroxide in a controlled manner and thus avoids the need to add the aqueous hydrogen peroxide slowly to the reaction mixture. The absence of water in the reaction media also resulted beneficial because it minimized undesired reactions of the oxidized product. A minimum amount of enzyme was necessary to show the catalytic effect. On recycling, the enzyme maintained its activity up to six rounds of epoxidations. A range of alkenes was epoxidized by this method providing yields ranging from 75 to 100 percent.

25 Introduction

25 Lipases (EC 3.1.1.3) catalyze the hydrolysis and synthesis of fatty acid ester bonds in triglycerides.¹ Organic chemists have exploited the ability of lipases to accept a wide variety of substrates and also non-natural acyl acceptors.² Lipase-mediated perhydrolysis of carboxylic acids in the presence of aqueous hydrogen peroxide was initially described by Björkling and co-workers in 1990.³ Hydrogen peroxide reacts with the acyl enzyme complex, formed by a fatty acid and the hydroxyl group of a serine aminoacid in the active site, to yield a peroxy-carboxylic acid. The peroxy-carboxylic acid released has been utilized as an *in situ* formed oxidant for the epoxidation of alkenes,^{3–6} in Baeyer–Villiger reactions,^{7,8} and also in the oxidation of sulfanyl to sulfinyl groups.^{3b} *Candida antarctica* lipase-B was found to efficiently catalyze the perhydrolysis of octanoic acid more effectively among a variety of lipases. The gene of *Candida antarctica* encoding for lipase-B has been cloned into a host microorganism, *Aspergillus oryzae*.⁹ The overexpressed enzyme has been immobilized in a macroporous polyacrylic resin by Novo Nordisk (Novozyme-435). Although several publications describe the lipase-based epoxidation with Novozyme-435,^{3–8} no optimization of reaction parameters has yet been reported. As part of our program in environmentally beneficial catalysis, we are interested in designing a “green” process to effectively carry out the epoxidation reaction. We report herein, an inexpensive, practical, safe and environmentally friendly method to oxidize a variety of alkenes under extremely mild conditions.

Results and discussion

25 One of the drawbacks in the original protocol reported by Björkling and co-workers,³ is the necessity to gradually add aqueous hydrogen peroxide to the reaction mixture over several hours to avoid lipase deactivation and to obtain higher conversions. To overcome this problem, we replaced the aq. hydrogen peroxide with urea–hydrogen peroxide complex (UHP) because of its potential to release the oxidant in a controlled manner.^{10,11} Other advantages of utilizing this anhydrous form of hydrogen peroxide include safer handling and minimal undesired hydrolysis of the epoxide products in the absence of water.

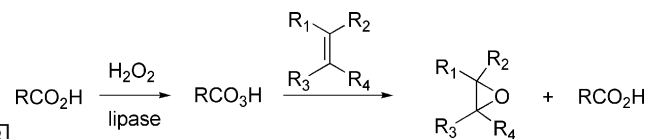
Effect of solvent

40 The lipase-mediated epoxidation of phenyl cyclohexene with a catalytic amount of octanoic acid was studied in different solvents employing UHP and 50% aq. hydrogen peroxide, Table 1. In general, reactions were faster when using aq. hydrogen peroxide than when using UHP. High conversions were observed when using low partition coefficient solvents,¹² except in the case of acetonitrile and diethyl ether. The lowest conversions were observed when using hydrocarbon solvents (entries 1–3) and diethyl ether (entry 8). The conversions in aromatic solvents were higher than in non-aromatic hydrocarbon solvents (entries 4 and 6). It is known that some esters can also be used as substrates in the lipase-mediated perhydrolysis; no octanoic acid was added when an ester was used as solvent (entry 9). High conversions were observed when ethyl acetate was employed with both oxidants. In this

^aDepartment of Chemical and Biochemical Engineering, The University of Iowa, Iowa City, IA 52242, USA

^bDivision of Medicinal and Natural Products Chemistry The University of Iowa, Iowa City, IA 52242, USA

† Electronic supplementary information (ESI) available: ¹H and ¹³C NMR spectra for 1–12. See DOI: 10.1039/b604984b



Scheme 1

Table 1 Epoxidation of phenylcyclohexene in different solvents

Entry	Solvent	Log P	% conversion UHP added	% conversion aq. 50% H ₂ O ₂ added
1	Hexane	3.5	14	39
2	Pentane	3.4	11	47
3	Cyclohexane	3.2	10	31
4	Toluene	2.5	35	66
5	Chloroform	2.2	21	75
6	Benzene	2.0	42	84
7	Dichloromethane	1.4	45	97
8	Diethyl ether	0.8	22	11
9	Ethyl acetate*	0.7	82	91
10	Acetonitrile	-0.3	42	27

^a Conditions: UHP (1 equiv.) or 50% aq H₂O₂ (1 equiv.), rt, octanoic acid (cat), time = 5 h. * No octanoic acid was added.

case, the presence of acetic acid was observed at the end of the reaction. We selected ethyl acetate to be the solvent of choice because of its low boiling point, ability to dissolve many substrates, highest conversion, environmentally friendliness, and non-toxicity. Interestingly, conversions using UHP in acetonitrile and diethyl ether were lower when using aq. hydrogen peroxide.^{3a}

Oxidant

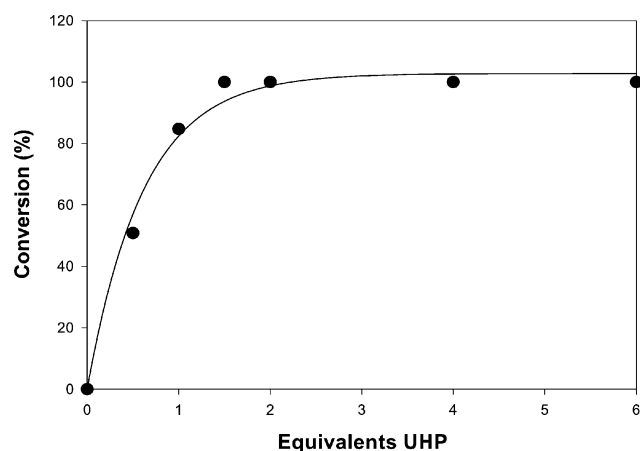
Bjorkling *et al.* reported that exposure of the enzyme to high concentrations of aq. hydrogen peroxide resulted in complete deactivation of the lipase.^{3a} Therefore, slow addition of aq. hydrogen peroxide to the reaction media was shown to increase the yields of peroxy-carboxylic acids. We found that replacement of the aq. hydrogen peroxide for UHP was beneficial. High concentrations of UHP had a positive effect on the chemo-enzymatic reaction (Fig. 1). However, one equivalent of UHP was enough to carry the reaction to completion.

Conditions

phenylcyclohexene, 1 mmol; ethyl acetate, 1.5 mL; Novozyme-435, 30 mg; time, 5 h.

Amount of enzyme

The conversion of phenylcyclohexene to the epoxide was carried out in ethyl acetate with different amounts of

**Fig. 1** Amount of UHP.**Table 2** Optimization of amount of enzyme

Entry	Amount of enzyme/mg	Time/h	Conversion (%)
1	50	5	82
2	40	5	86
3	25	5	86
4	15	5	85
5	10	5	85
6	5	5	86
7	2	5	81
8	1	5	61
9	No enzyme	65	0

Novozyme-435 and determined by ¹H NMR spectroscopy, Table 2. Interestingly, similar conversions were observed even when the amount of enzyme was minimal. No appreciable amount of epoxide was detected when the experiment was conducted in the absence of lipase.

Examination of enzyme recycle

The re-use of Novozyme-435 was investigated to assess the economic potential of the process, Fig. 2. The lipase was washed with acetonitrile–water (9 : 1) to remove urea, and washed with ethyl acetate after each cycle. The activity of the lipase was retained in the first two cycles. Conversion decreased to 81–85% after three cycles. The enzyme was recycled six times without appreciable loss of activity. The ability to recycle the immobilized lipase is important to implement a low cost process. In contrast, when aq. hydrogen peroxide was employed, the activity of the enzyme was lost after the second cycle.

General procedure

A general procedure was applied to the oxidations of a variety of olefins, Table 3. The reaction was carried out employing 1.1 equiv. of UHP, and a small amount of Novozyme-435 with a variety of olefins dissolved in ethyl acetate. Oxidation of cyclic olefins furnished the corresponding epoxides in very good and excellent yields (entries 1–6). Epoxidations of norbornene and α -pinene (entries 5 and 6) were completely

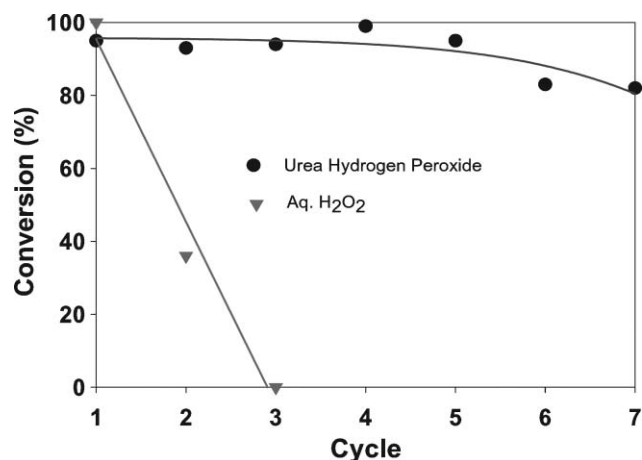
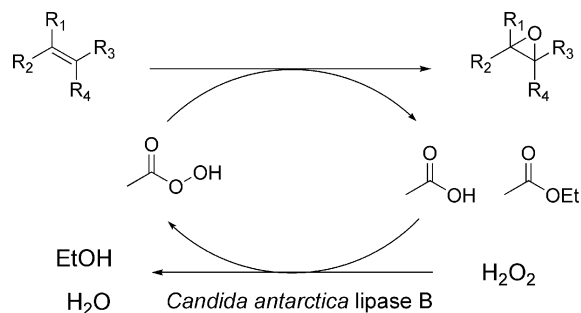
**Fig. 2** Enzyme recycling.

Table 3 Epoxidation of different alkenes

Entry	Alkene	Epoxide	Time/h	Yield (%)
1	Cyclohexene		40	83
2	1-Methylcyclohexene		2	100
3	1-Phenylcyclohexene		28	100
4	Cyclooctene		11	100
5	Norbornene		60	90
6	α -Pinene		5.5	95
7	1-Hexene		161	73
8	1-Octene		46	85
9	Styrene		33	81
10	α -Methylstyrene		46	90
11	β -Methylstyrene		46	86
12	Indene		50	77

stereoselective, furnishing the oxirane ring exclusively on the less hindered side of the olefins in high yields.¹³ Oxidation of terminal olefins of lineal hydrocarbons is known to be slow (entries 7 and 8).¹⁴ Oxidation of olefins bonded to aromatics was also successful (entries 9–12).

Conclusion

We presented a general and practical chemo-enzymatic procedure for the oxidation of a variety of olefins which minimizes the use of enzyme. The method employs an oxidant which is safer to handle than aq. hydrogen peroxide, utilizes an environmentally friendly solvent and generates peracetic acid *in situ*. The resulting epoxides were obtained in very good to excellent yields using stoichiometric amounts of UHP and catalytic amounts of Novozyme-435 in ethyl acetate. Studies on the asymmetric version of this chemo-enzymatic procedure are currently underway in our laboratory.

Experimental

Effect of solvent

The experiments were performed with 1 mmol of the alkene, 1.1 mmol of UHP, 50 mg of Novozyme-435, and 3 ml of the corresponding solvent. The reaction was shaken in a test tube sealed with a cap in a shake-table at 27 °C and 250 rpm. The reaction was stopped after 5 h and filtered through a cotton plug. The solvent was evaporated and the residue was analyzed by ¹H NMR to determine the ratio of alkene to epoxide. The residue was dissolved in ethyl acetate and washed with water and aq. sat. soln of NaHCO₃ to remove urea and acid.

General procedure for the epoxidation of olefins

A solution of the olefin (1 mmol) in ethyl acetate (1.5 mL) was added urea–hydrogen peroxide (1.1 mmol) and Novozyme-435 (50 mg). The mixture was shaken in a test tube closed with a cap in a shake-table at 250 rpm for the time as shown in Table 4. The solution was filtered through a small piece of cotton and the solid washed with more ethyl acetate. The filtrate was washed with water, dried over Na₂SO₄, filtered and the solvent evaporated under reduced pressure. The products were analyzed by ¹H and ¹³C NMR.

Cyclohexene oxide, 1. ¹H NMR (CDCl₃): δ 3.13 (2H, m), 2.00–1.91 (2H, m), 1.86–1.76 (2H, m), 1.49–1.36 (2H, m), 1.31–1.16 (2H, m); ¹³C NMR (CDCl₃): δ 52.3 (2CH), 24.6 (2CH₂), 19.6 (2CH₂).

1-Methylcyclohexene oxide, 2. ¹H NMR (CDCl₃): δ 2.95 (1H, br s), 1.95–1.78 (3H, m), 1.66 (1H, m), 1.48–1.34 (2H, m), 1.30 (3H, d, J = 1.8 Hz), 1.32–1.10 (2H, m); ¹³C NMR (CDCl₃): δ 59.7 (CH), 57.6 (C), 30.0 (CH), 24.9 (CH₃), 24.1 (CH₂), 20.2 (CH₂), 19.8 (CH₂).

Phenylcyclohexene oxide, 3. ¹H NMR (CDCl₃): δ 7.40–7.21 (5H, m), 3.06 (1H, s), 2.27 (1H), 2.11 (1H), 1.98 (2H, m), 1.66–1.24 (4H, m); ¹³C NMR (CDCl₃): δ 142.6 (C), 128.4 (2CH₂), 127.3 (CH), 125.4 (2CH₂), 62.0 (CH), 60.3 (C), 29.0 (CH₂), 24.8 (CH₂), 20.2 (CH₂), 19.9 (CH₂).

Cyclooctene oxide, 4. ¹H NMR (CDCl₃): δ 2.93–2.87 (2H, m), 2.19–2.10 (2H, m), 1.68–1.39 (8H, m), 1.35–1.21 (2H, m); ¹³C NMR (CDCl₃): δ 55.7 (2CH), 26.7 (2CH₂), 26.4 (2CH₂), 25.7 (2CH₂).

1 **exo-Norbornene oxide, 5.** ^1H NMR (CDCl_3): δ 3.06 (2H, s),
2.44 (2H, s), 1.48 (2H, m), 1.31 (1H, m), 1.21 (2H, m), 0.70
(1H, d, $J = 9.9$ Hz); ^{13}C NMR (CDCl_3): δ 51.6 (2CH), 36.8
5 (2CH), 26.4 (CH_2), 25.3 (2CH_2).

α -Pinene oxide, 6. ^1H NMR (CDCl_3): δ 3.07 (1H, m), 2.06–
1.90 (4H, m), 1.73 (1H, m), 1.62 (1H, m), 1.35 (3H, s), 1.30
(3H, s), 0.94 (3H, s); ^{13}C NMR (CDCl_3): δ 60.5 (C), 57.0 (CH),
45.2 (CH), 40.7 (C), 39.9 (CH), 27.8 (CH_2), 26.8 (CH_3), 26.0
10 (CH_2), 22.5 (CH_3), 20.3 (CH_3).

1-Hexene oxide, 7. ^1H NMR (CDCl_3): δ 2.91 (1H, m), 2.75
(1H, dd, $J = 5.0, 4.0$ Hz), 2.47 (1H, dd, $J = 5.1, 2.7$ Hz), 1.58–
1.26 (6H, m), 0.92 (3H, t, $J = 6.7$ Hz); ^{13}C NMR (CDCl_3): δ
15 52.6 (CH), 47.3 (CH_2), 32.4 (CH_2), 28.3 (CH_2), 22.7 (CH_2),
14.2 (CH_3).

1-Octene oxide, 8. ^1H NMR (CDCl_3): δ 2.92 (1H, m), 2.76
(1H, t, $J = 4.6$ Hz), 2.48 (1H, dd, $J = 5.1, 2.7$ Hz), 1.58–1.27
20 (10H, m), 0.90 (3H, t, $J = 7.0$ Hz); ^{13}C NMR (CDCl_3): δ 52.6
(CH), 47.3 (CH_2), 32.7 (CH_2), 31.9 (CH_2), 29.3 (CH_2), 26.1
(CH_2), 22.7 (CH_2), 14.2 (CH_3).

Styrene oxide, 9. ^1H NMR (CDCl_3): δ 7.39–7.26 (5H, m),
25 3.87 (1H, dd, $J = 4.0, 2.6$ Hz), 3.15 (1H, dd, $J = 5.5, 4.1$ Hz),
2.81 (1H, dd, $J = 5.5, 2.6$ Hz); ^{13}C NMR (CDCl_3): δ 137.8 (C),
128.7 (2CH), 128.4 (CH), 125.7 (2CH), 52.6 (CH), 51.4 (CH_2).

α -Methylstyrene oxide, 10. ^1H NMR (CDCl_3): δ 7.38–7.23
30 (5H, m), 2.95 (1H, d, $J = 5.5$ Hz), 2.78 (1H, dq, $J = 5.5, 0.8$ Hz),
1.71 (3H, t, $J = 0.7$ Hz); ^{13}C NMR (CDCl_3): δ 141.3 (C), 128.5
(2CH), 127.6 (CH), 125.4 (2CH), 57.1 (CH), 56.9 (C), 21.9
(CH_3).

β -Methylstyrene oxide, 11. ^1H NMR (CDCl_3): δ 7.34–7.21
35 (5H, m), 3.55 (1H, d, $J = 2.0$ Hz), 3.01 (1H, dq, $J = 5.1, 2.0$ Hz),
1.42 (3H, t, $J = 5.1$ Hz); ^{13}C NMR (CDCl_3): δ 137.9 (C), 128.5
(2CH), 128.1 (CH), 125.6 (2CH), 59.6 (CH), 59.1 (CH), 18.0
40 (CH_3).

Indene oxide, 12. ^1H NMR (CDCl_3): δ 7.47 (1H, d, $J =$
7.2 Hz), 7.26–7.14 (3H, m), 4.23 (1H, d, $J = 2.8$ Hz), 4.09 (1H,
t, $J = 2.8$ Hz), 3.18 (1H, d, $J = 18$ Hz), 2.93 (1H, dd, $J = 17.9,$

2.9 Hz); ^{13}C NMR (CDCl_3): δ 143.6 (C), 140.9 (C), 128.6
(CH), 126.2 (CH), 126.1 (CH), 125.2 (CH), 59.1 (CH), 57.7
(CH), 34.6 (CH_2).

Acknowledgements

This research was supported by research grant EEC-0310689
from the National Science Foundation.

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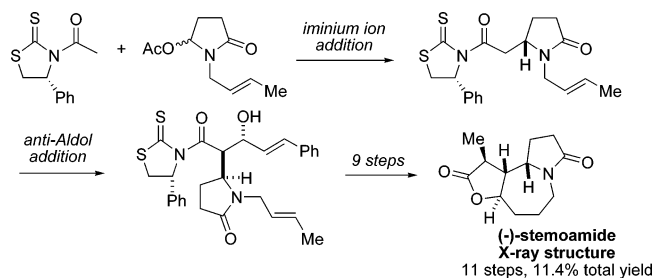
Synthesis of (–)-Stemoamide Using a Stereoselective *anti*-Aldol Step

Horacio F. Olivo,* Ricardo Tovar-Miranda, and Efraín Barragán

Division of Medicinal and Natural Products Chemistry, College of Pharmacy, The University of Iowa, Iowa City, Iowa 52242

horacio-olivo@uiowa.edu

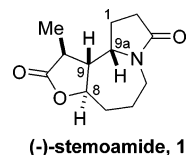
Received November 15, 2005



The synthesis of (–)-stemoamide was achieved in 11 steps from 5-acetoxy-*N*-crotyl pyrrolidinone. A chiral *N*-acyl thiazolidinethione was employed in a stereoselective addition to a cyclic *N*-acyl iminium ion to install the required stereochemistry of carbon C9a. This iminium ion addition product was employed in a stereoselective MgBr₂-catalyzed *anti*-aldol reaction to install the required stereochemistry of carbons C8 and C9. The X-ray crystal analysis of (–)-stemoamide confirmed the structure and the stereochemical outcome of these selective reactions.

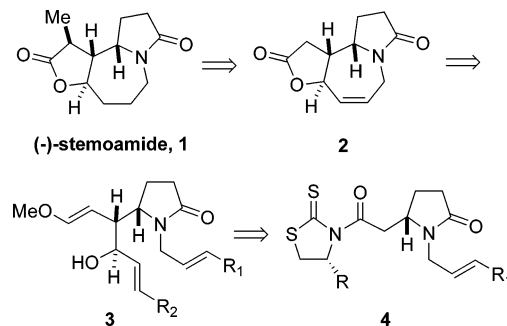
The *Stemonaceae* plant family is a rich source of bioactive alkaloids with more than 70 alkaloids isolated to date.¹ The rhizomes and root extracts of these plants have been used in traditional Chinese and Japanese folk medicine as insecticides, as vermifuges, and also for the treatment of respiratory diseases such as bronchitis, pertussis, and tuberculosis. (–)-Stemoamide (**1**) was isolated from the roots and rhizomes of *Stemona tuberosa* by Xu et al., in 1992.² Stemoamide is one of the structurally simplest members of the *Stemona* family possessing a γ -lactone fused to a pyrrolo[1,2*a*]azepine nucleus. Several syntheses of racemic and natural stemoamide have been achieved to date^{3,4} as well as have several approaches to the

tricyclic core.⁵ With the exception of Jacobi's seven-step synthesis of stemoamide,^{3d,4b} syntheses of stemoamide either are too long or lack a complete stereochemical control during the installation of the contiguous stereocenters and consequently require extra steps to correct their stereochemistry. As part of our program in the synthesis and pharmacology of *Stemona* alkaloids with unique biological properties,⁶ we sought to develop enantioselective strategies which will allow us to prepare large amounts of these alkaloids. As a first step toward this goal, we embarked on a practical synthesis of (–)-stemoamide.



We envisioned a synthetic strategy of (–)-stemoamide that relied on installing the correct stereochemistry of the three contiguous stereocenters C8, C9, and C9a employing a chiral thiazolidinethione as illustrated in Scheme 1. Conversion of the

SCHEME 1. Retrosynthetic Analysis of (–)-Stemoamide



hydrogenated product of **2** to stemoamide is well precedented.^{3f,4a} The lactone ring would be prepared from Wittig olefination product **3**, and the azepine ring would be formed by a ring-closing olefin metathesis (RCM). Installing the correct stereochemistry of C8 and C9 would require an *anti*-aldol reaction of *N*-acyl thiazolidinethione **4**, and introducing the stereochemistry of C9a would require the addition of a chiral *N*-acetyl imine to a cyclic iminium ion.

We recently reported the stereoselective addition of the titanium(IV) enolate of *N*-acetyl-4*S*-isopropylthiazolidinethiones to cyclic *N*-acyl iminium ions.⁷ Addition of a metal enolate derived from *N*-acetyl thiazolidinethione to a cyclic *N*-acyl imine creates a stereocenter with stereochemistry opposite of the one

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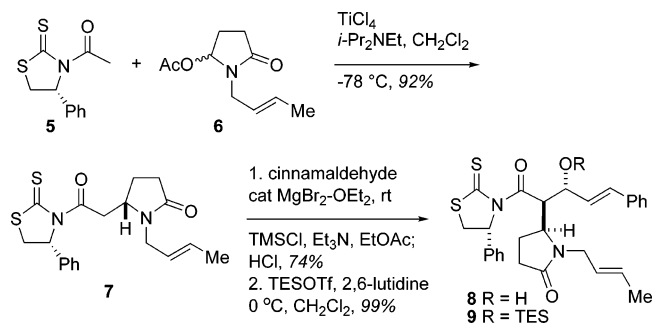
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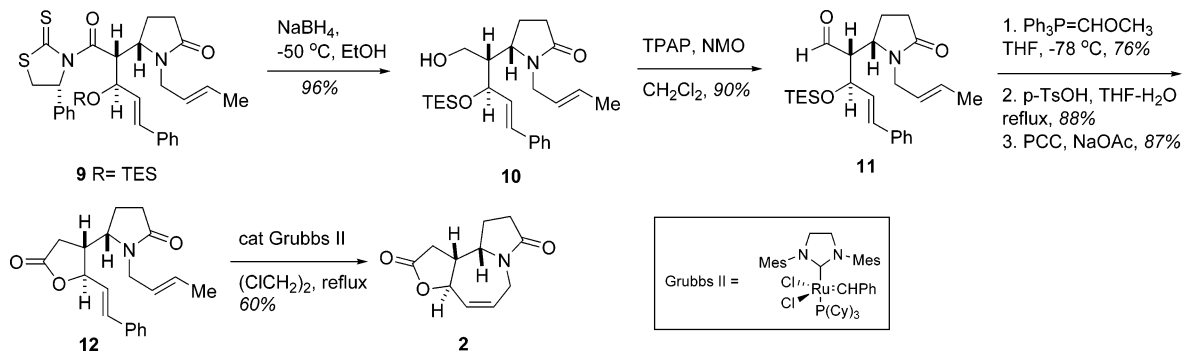
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SCHEME 2. Chiral Thiazolidinethione-Directed Addition to Iminium Ion and *anti*-Aldol


obtained when added to an *N*-acyl iminium ion using the same chiral auxiliary.^{8,9} Because *N*-acetyl-4*R*-isopropylthiazolidinethione would be too costly to prepare, we selected the 4*R*-phenyl thiazolidinethione **5** for the construction of the required stereochemistry of C9a as found in natural stemoamide (Scheme 2). Addition of the titanium enolate of **5** to the iminium ion formed from 5-acetoxy pyrrolidinone **6**¹⁰ gave the desired diastereomeric product **7** in 92% isolated yield after column chromatography.

A highly diastereoselective *anti*-aldol reaction employing chiral thiazolidinethione auxiliaries was recently disclosed by Evans.¹¹ The reaction is catalytic in magnesium salts and is facilitated by silylation with chlorotrimethylsilane at room temperature. We reported this *anti*-aldol reaction when the aldehyde employed was cinnamaldehyde and the *N*-acyl thiazolidinethione was the addition product of the titanium(IV) enolate of *N*-acetyl-4*S*-isopropylthiazolidinethione with *N*-crotyl-5-acetoxy pyrrolidinone.⁷ An X-ray crystallographic analysis confirmed the stereochemical output of the reaction. When thiazolidinethione **7** was employed in the *anti*-aldol reaction with acrolein, no reaction was observed. However, when the aldehyde employed was cinnamaldehyde, aldol product **8** was obtained in 74% yield after column chromatography (Scheme 2). Because the reactions were carried out with the 4*S*-substituted thiazolidinethione instead of with the 4*R*-isomer, as previously described,⁷ we presumed aldol product **8** had a stereochemistry opposite of the product obtained when using the 4*R*-isomer. Thus, aldol product **8** possesses the required stereochemistry of carbons C8, C9, and C9a for the synthesis of (–)-stemoamide. Aldol product **8** was protected as the triethylsilyl ether **9** in quantitative yield.

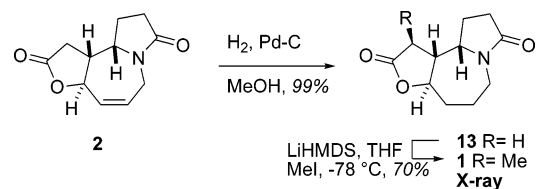
Homologation of the acyl group of **9** to form the γ -lactone and RCM to form the azepine ring are illustrated in Scheme 3. Although many chiral thiazolidinethiones can be reduced directly

SCHEME 3. Homologation and Azepine Construction


to the corresponding aldehyde,¹² we were unable to partially reduce thiazolidinethione **9** to aldehyde **11** in good yields. However, reduction of thiazolidinethione with sodium borohydride occurred in 96% yield, and oxidation of the alcohol **10** to aldehyde **11** occurred in 90% yield.

Aldehyde **11** was reacted with the phosphonium salt $\text{Ph}_3\text{P}^+\text{CH}_2\text{OCH}_3\text{Cl}^-$ in the presence of NaHMDS to give an inseparable *E,Z*-mixture of methylvinyl ethers; under acidic conditions, the silyl ether was removed and the methylvinyl ether was hydrolyzed to deliver a diastereomeric mixture of lactols in 88% yield. Oxidation of the lactols with PCC gave the desired lactone **12** in very good yield. Although many combinations of dienes have been reported in ring-closing olefin metathesis (RCM), we found no RCM literature precedent with vinylic methyl and phenyl groups.¹³ We found that RCM using the second generation of Grubbs' catalyst (Grubbs II) in refluxing 1,2-dichloroethane furnished azepine **2** in 60% yield.

The two remaining steps to complete the total synthesis are illustrated in Scheme 4. Palladium-catalyzed hydrogenation of

SCHEME 4. Completion of the Synthesis


the unsaturated azepine **2** gave compound **13** in almost quantitative yield. Stereoselective methylation of C10 on the less-hindered face of lactone **13** at low temperature gave stemoamide **1** in 70% yield, as previously reported by Narasaka^{4a} and Sibi.^{3f} All spectroscopic data and physical data of stemoamide were in agreement with the published data.^{2,3} The X-ray crystallographic analysis of (–)-stemoamide confirmed the stereochemistry of the product as envisioned in the synthetic plan.

In summary, we have achieved a synthesis of (–)-stemoamide in 11 steps starting from easily prepared starting materials (14% overall yield). We have demonstrated the utility of the stereoselective addition of a titanium(IV) enolate of *N*-acetyl thiazolidinethione to a cyclic iminium ion and the use of the same chiral auxiliary to control the stereochemistry in a MgBr_2 -catalyzed *anti*-aldol reaction for the synthesis of (–)-stemoamide. The structure of (–)-stemoamide was confirmed by X-ray crystallographic analysis.

Experimental Section

(-)-5(S)-[2-(4(R)-Phenyl-2-thioxo-thiazolidine-3-yl)-2-oxo-ethyl]-1-(but-2-enyl)-pyrrolidine-2-one **7**. A solution of TiCl_4 (1 M in CH_2Cl_2 , 1.5 mL, 1.5 mmol) was added to a solution of *N*-acetyl-4(R)-phenyl thiazolidinethione (356 mg, 1.5 mmol) in CH_2Cl_2 (5 mL) cooled to 0 °C. The solution was stirred for 5 min and then cooled to -30 °C. The reaction mixture was treated with a solution of diisopropylethylamine (220 mg, 1.7 mmol) in CH_2Cl_2 (5 mL). The reaction mixture was stirred for 40 min and cooled to -78 °C. A solution of 5-acetoxy *N*-crotyl pyrrolidine-2-one (395 mg, 2.0 mmol) in CH_2Cl_2 (5 mL) was added to the reaction mixture via cannula. The reaction mixture was stirred and warmed to 0 °C for 6 h. The reaction was quenched by addition of saturated $\text{NH}_4\text{-Cl}$ solution and stirred for 5 min. The aqueous layer was extracted with CH_2Cl_2 (2 × 25 mL). The combined organic layer was then washed with saturated NaHCO_3 and brine. The organic layer was dried over Na_2SO_4 , filtered, concentrated in vacuo, and purified by silica gel column chromatography (CHCl_3 -EtOAc-petroleum ether, 4:2:1) to afford 516 mg of **7** as a yellow oil (92% yield): R_f 0.35 (CHCl_3 -EtOAc-Petroleum Ether, 4:2:1); $[\alpha]_D^{25} = -359$ (c 1.0, CHCl_3); IR 3002, 1683, 1377, 1332, 1259, 1159 cm^{-1} ; $^1\text{H NMR}$ (CDCl_3) δ 7.44–7.33 (5H, m), 6.22 (1H, d, $J = 8.2$ Hz), 5.57 (1H, dq, $J = 15.2$, 6.4 Hz), 5.32 (1H, m), 4.07 (2H, bs), 3.96 (1H, dd, $J = 11.3$, 8.3 Hz), 3.90 (1H, dd, $J = 17.6$, 3.3 Hz), 3.52 (1H, dd, $J = 15.2$, 7.0 Hz), 3.16 (1H, dd, $J = 17.5$, 9.8 Hz), 3.09 (1H, dd, $J = 10.4$, 1.5 Hz), 2.48–2.17 (3H, m), 1.66 (3H, d, $J = 6.4$ Hz), 1.63 (1H, m); $^{13}\text{C NMR}$ (CDCl_3) δ 202.4 (C), 174.7 (C), 170.9 (C), 139.1 (C), 129.5 (CH), 129.3 (2CH), 128.9 (CH), 125.6 (2CH), 125.4 (CH), 69.7 (CH), 54.3 (CH), 42.7 (2CH₂), 36.6 (CH₂), 29.7 (CH₂), 24.6 (CH₂), 17.7 (CH₃).

1-(4R-Phenyl-2-thioxo-1,3-thiazolidin-3-yl)-(2S,3R)-3-hydroxy-2-(1-but-2-enyl-5-oxo-pyrrolidin-2(S)-yl)-5-phenyl-pent-4-en-1-one **8**. To a solution of compound **7** (748 mg, 2 mmol) in ethyl acetate (6 mL) was added $\text{MgBr}_2 \cdot \text{OEt}_2$ (78 mg, 0.3 mmol), cinnamaldehyde (0.278 mL, 2.2 mmol), triethylamine (0.558 mL, 4 mmol), and TMSCl (0.381 mL, 3 mmol). The mixture was stirred at room temperature for 36 h. The reaction was filtered through a plug of silica and eluted with ethyl acetate. The eluent was concentrated in vacuo, and the residue was dissolved in 20 mL of THF and 5 mL of 1 N HCl. After stirring for 1 h at room temperature, the mixture was diluted with 100 mL of AcOEt and 100 mL of water. The phases were separated, and the organic layer was washed with a saturated solution of NaHCO_3 (2 × 30 mL) and brine (2 × 30 mL), dried over Na_2SO_4 , filtered, and concentrated in vacuo. The residue was purified by column chromatography on silica gel eluting with petroleum ether-acetone (7:3, 6:4, 5:5, and 4:6): 772 mg (74% yield); R_f 0.32 (4:2:1, chloroform-ethyl acetate-petroleum ether); $[\alpha]_D^{25} = -331$ (c 1.0, CHCl_3); IR 3345, 2937, 1669, 1449, 1256, 1161 cm^{-1} ; $^1\text{H NMR}$ (CDCl_3) δ

7.43–7.24 (10H, m), 6.64 (1H, dd, $J = 16.0$, 1.7 Hz), 6.23 (1H, dd, $J = 16.0$, 4.0 Hz), 5.95 (1H, d, $J = 7.8$ Hz), 5.33 (1H, m), 5.32 (1H, dd, $J = 6.8$, 3.6 Hz), 5.21 (1H, m), 4.63 (1H, bs), 4.29 (1H, m), 4.17 (1H, dd, $J = 15.2$, 5.6 Hz), 3.38 (1H, dd, $J = 11.2$, 8.1 Hz), 3.23 (1H, dd, $J = 15.2$, 6.6 Hz), 2.94 (1H, dd, $J = 11.2$ Hz), 2.60 (1H, dt, $J = 17.0$, 9.2 Hz), 2.30 (1H, dd, $J = 9.7$, 3.5 Hz), 2.01 (1H, m), 1.66 (1H, m), 1.58 (3H, d, $J = 6.2$ Hz); $^{13}\text{C NMR}$ (CDCl_3) δ 203.1 (CS), 175.6 (CO), 174.3 (CO), 138.8 (C), 136.2 (C), 130.0 (CH), 129.8 (CH), 129.6 (CH), 129.3 (2CH), 129.0 (CH), 128.9 (CH), 128.3 (CH), 126.5 (2CH), 125.6 (2CH), 124.9 (CH), 70.5 (CH), 70.2 (CH), 56.9 (CH), 50.4 (CH), 43.1 (CH₂), 36.7 (CH₂), 30.1 (CH₂), 21.8 (CH₂), 17.9 (CH₃).

TES-Protected Aldol Product 9. To a dichloromethane solution cooled to -50 °C was added TESOTf (0.2 mL, 0.89 mmol) and 2,6-lutidine (0.1 mL, 0.89 mmol). After the solution was stirred for 15 min, the alcohol **8** dissolved in dichloromethane was added via cannula. The reaction mixture was warmed to room temperature overnight. The solution was washed with saturated Na_2CO_3 . The organic layer was dried over Na_2SO_4 , filtered, and concentrated in vacuo. The residue was purified by silica gel column chromatography (petroleum ether/ethyl acetate, 7:3) to give 366 mg (99%). R_f 0.34 (7:3, petroleum ether-ethyl acetate); $[\alpha]_D^{25} = -286$ (c 1.0, CHCl_3); IR 2955, 2911, 1690, 1161 cm^{-1} ; $^1\text{H NMR}$ (CDCl_3) δ 7.41–7.22 (10H, m), 6.55 (1H, d, $J = 15.9$ Hz), 6.16 (1H, dd, $J = 15.8$, 7.2 Hz), 6.08 (1H, d, $J = 7.9$ Hz), 5.52 (1H, m), 5.48 (1H, dq, $J = 6.9$, 4.9 Hz), 5.24 (1H, m), 4.68 (1H, t, $J = 7.1$ Hz), 4.14 (2H, m), 3.74 (1H, dd, $J = 11.3$, 8.0 Hz), 3.22 (1H, dd, $J = 15.3$, 7.2 Hz), 3.01 (1H, d, $J = 11.3$ Hz), 2.28 (3H, m), 1.98 (1H, m), 1.62 (3H, d, $J = 6.3$ Hz), 0.96 (9H, t, $J = 8$ Hz), 0.62 (6H, q, $J = 7.8$ Hz); $^{13}\text{C NMR}$ (CDCl_3) δ 203.1 (C), 175.3 (C), 172.7 (C), 139.1 (C), 136.2 (C), 131.6 (CH), 129.9 (CH), 129.2 (CH), 129.1 (2CH), 128.9 (2CH), 128.6 (CH), 128.2 (CH), 126.7 (2CH), 125.4 (2CH), 125.3 (CH), 73.3 (CH), 70.4 (CH), 56.0 (CH), 52.1 (CH), 43.0 (CH₂), 37.1 (CH₂), 30.4 (CH₂), 21.1 (CH₂), 17.9 (CH₃), 7.0 (3CH₃), 5.3 (3CH₂).

Alcohol 10. To a solution of thiazolidinethione **9** (257 mg, 0.414 mmol) in dry ethanol (4 mL) cooled to -15 °C was added NaBH_4 (32 mg, 0.86 mmol). The reaction was stirred at 4 °C overnight. Excess borohydride was quenched at 0 °C with diluted HCl and concentrated. The residue was partitioned between water and ether, and the organic layer was separated and washed with saturated Na_2CO_3 and brine, dried over Na_2SO_4 , filtered, and concentrated in vacuo. The residue was purified by column chromatography on silica gel (petroleum ether/ethyl acetate, 7:3) to give 177 mg of **10** (96%) as a colorless oil: R_f 0.22 (1:1, petroleum ether-ethyl acetate); $[\alpha]_D^{25} = -17$ (c 1.0, CHCl_3); IR 3405, 2955, 1668, 1449, 1422 cm^{-1} ; $^1\text{H NMR}$ (CDCl_3) δ 7.39–7.24 (5H, m), 6.50 (1H, d, $J = 15.9$ Hz), 6.28 (1H, dd, $J = 15.9$, 6.5 Hz), 5.61 (1H, dq, $J = 15.3$, 6.5 Hz), 5.35 (1H, m), 4.54 (1H, dd, $J = 7.6$, 3.2 Hz), 4.40 (1H, ddt, $J = 15.0$, 4.9, 1.5 Hz), 3.99–3.89 (2H, m), 3.78 (1H, m), 3.44 (1H, dd, $J = 15.0$, 7.8 Hz), 3.11 (1H, bs), 2.45 (1H, m), 2.35 (1H, m), 2.24–2.08 (2H, m), 1.86 (1H, m), 1.66 (3H, d, $J = 6.5$ Hz), 0.96 (9H, t, $J = 8.0$ Hz), 0.62 (6H, q, $J = 8.0$ Hz); $^{13}\text{C NMR}$ (CDCl_3) δ 175.7 (C), 136.3 (C), 131.2 (CH), 131.0 (CH), 129.6 (CH), 128.9 (2CH), 128.2 (CH), 126.7 (2CH), 125.5 (CH), 74.6 (CH), 61.5 (CH₂), 57.1 (CH), 48.1 (CH), 43.4 (CH₂), 30.4 (CH₂), 22.5 (CH₂), 17.9 (CH₃), 6.9 (3CH₃), 5.2 (3CH₂).

Aldehyde 11. To a solution of alcohol **10** (95 mg, 0.22 mmol) in 9.5 mL of DCM was added molecular sieves (170 mg), 4-methylmorpholine *N*-oxide (47 mg, 0.4 mmol), and TPAP (7 mg, 0.02 mmol). The mixture was stirred at room temperature and followed by TLC. After 1 h, the reaction was completed and it was filtered through a short column of silica gel and eluted with acetone to give 85 mg (90%) of aldehyde **11**: R_f 0.5 (1:1, petroleum ether-ethyl acetate); $[\alpha]_D^{25} = -90.8$ (c 1.0, CHCl_3); IR 2954, 2361, 1690, 1454, 1418, 1244 cm^{-1} ; $^1\text{H NMR}$ (CDCl_3) δ 10.00 (1H, d, $J = 1.6$ Hz), 7.40–7.25 (5H, m), 6.56 (1H, d, $J = 15.8$ Hz), 6.34 (1H, dd, $J = 15.8$, 8.1 Hz), 5.59 (1H, dq, $J = 15.3$, 6.4

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(Hz), 5.33 (1H, m), 4.67 (1H, dd, $J = 8.2, 3.3$ Hz), 4.31 (1H, ddt, $J = 15.2, 5.3, 1.5$ Hz), 4.20 (1H, dd, $J = 11.6, 6.6$ Hz), 3.30 (1H, dd, $J = 15.2, 7.6$ Hz), 2.75 (1H, m), 2.56–2.31 (2H, m), 2.24–2.16 (2H, m), 1.66 (3H, dd, $J = 6.5, 0.9$ Hz), 0.93 (9H, t, $J = 8.0$ Hz), 0.60 (6H, q, $J = 7.8$ Hz); ^{13}C NMR (CDCl_3) δ 201.8 (CH), 175.5 (C), 135.8 (C), 132.0 (CH), 130.0 (CH), 129.8 (CH), 128.9 (2CH), 128.4 (CH), 126.7 (2CH), 125.1 (CH), 71.6 (CH), 59.4 (CH), 55.8 (CH), 43.2 (CH_2), 30.2 (CH_2), 21.4 (CH_2), 17.8 (CH_3), 6.9 (3CH_3), 5.3 (3CH_2).

Lactone 12. To a suspension of $\text{MeOCH}_2\text{PPh}_3\text{Cl}$ (1.100 g, 3.2 mmol) in dry THF (10 mL) at -78°C was added NaHMDS (1 M in THF, 2.68 mL, 2.68 mmol) dropwise, and the mixture was stirred for 20 min. Aldehyde **11** (458 mg, 1.071 mmol) in dry THF (1 mL) was added dropwise to the reaction mixture. The reaction was stirred for 3 h at -78°C and then allowed to warm to room temperature. The reaction was quenched with NH_4Cl (saturated, 5 mL), and the mixture was extracted with ethyl acetate. The organic layer was dried over Na_2SO_4 , filtered, and concentrated in vacuo. The residue was purified by column chromatography (petroleum ether/ethyl acetate, 3:2) to yield the Wittig product as a mixture of geometric isomers (371 mg, 76%). The Wittig product (334 mg, 0.733 mmol) was dissolved in $\text{THF}-\text{H}_2\text{O}$ (16 mL, 3:1), and *p*-TsOH (140 mg, 0.733 mmol) was added. The mixture was refluxed for 4 h. The reaction was allowed to cool to room temperature and treated with NaHCO_3 . The reaction mixture was extracted with dichloromethane. The organic layer was dried over Na_2SO_4 , filtered, and concentrated in vacuo. The residue was purified by column chromatography (petroleum ether/acetone, 6:4) to give 210 mg of a mixture of lactols (88%) as colorless oil. To a solution of lactols (200 mg, 0.61 mmol) in dichloromethane (60 mL) was added PCC (263 mg, 1.22 mmol) and sodium acetate (132 mg, 1.6 mmol). The mixture was stirred for 6 h at room temperature. The reaction was diluted with AcOEt (20 mL), filtered on a small column of silica gel (5 cm), and washed with dichloromethane. The solvent was evaporated to give lactone **12** (173 mg, 87%): R_f 0.43 (petroleum ether–ethyl acetate, 1:4); $[\alpha]_D^{25} = +70.1$ (*c* 1.0, CHCl_3); IR 3025, 2928, 1777, 1684, 1424, 1171, 971 cm^{-1} ; ^1H NMR (CDCl_3) δ 7.40–7.28 (5H, m), 6.64 (1H, d, $J = 15.8$ Hz), 6.11 (1H, dd, $J = 15.8, 7.0$ Hz), 5.64 (1H, dq, $J = 15.3, 6.4$ Hz), 5.33 (1H, m), 4.89 (1H, dd, $J = 7.1, 3.3$ Hz), 4.34 (1H, d, $J = 15.3$ Hz), 3.84 (1H, m), 3.34 (1H, dd, $J = 15.2, 7.6$ Hz), 2.89–2.77 (2H, m), 2.57–2.32 (3H, m), 2.24–2.11 (1H, m), 1.89–1.77 (1H, m), 1.67 (3H, d, $J = 6.3$ Hz); ^{13}C NMR (CDCl_3) δ 175.4 (C), 175.2 (C), 135.4 (C), 133.9 (CH), 130.3 (CH), 128.9 (2CH), 128.3 (CH), 127.0 (2CH), 125.6 (CH), 125.1 (CH), 80.5 (CH), 58.2 (CH), 43.2 (CH_2), 42.1 (CH), 31.0 (CH_2), 30.1 (CH_2), 20.1 (CH_2), 17.9 (CH_3).

RCM Product 2. To a solution of diene **12** (26 mg, 80 μmol) in ethylene dichloride (10 mL) was added Grubb's catalyst second generation (6.8 mg, 8 μmol) dissolved in ethylene dichloride (6 mL) over 5 h. The reaction mixture was stirred at 110°C for 20 h. The reaction was filtered on a plug of silica gel using acetone as solvent. The solvent was evaporated, and the residue was purified by column chromatography (methanol–dichloromethane, 5:95) to give metathesis product **2** (10 mg, 60%): R_f 0.29 (methanol–

dichloromethane, 5:95); IR 3456, 2920, 1783, 1683, 1418, 1276, 1183, 1023 cm^{-1} ; ^1H NMR (CDCl_3) δ 5.93 (1H, d, $J = 11.3$ Hz), 5.76 (1H, dddd, $J = 11.3, 6.0, 2.3, 1.8$ Hz), 5.03 (1H, dq, $J = 10.5, 1.7$ Hz), 4.74 (1H, dd, $J = 18.4, 6.0$ Hz), 4.10 (1H, dt, $J = 9.8, 6.6$ Hz), 3.45 (1H, bd, $J = 18.4$ Hz), 3.13 (1H, m), 2.70–2.46 (4H, m), 2.12 (1H, m), 2.12 (1H, m), 1.77 (1H, m); ^{13}C NMR (CDCl_3) δ 175.5 (C), 173.9 (C), 129.4 (CH), 128.6 (CH), 78.1 (CH), 57.0 (CH), 44.9 (CH), 40.7 (CH_2), 31.1 (CH_2), 30.9 (CH_2), 21.2 (CH_2); *m/e* calcd for $\text{C}_{11}\text{H}_{14}\text{NO}_3$ 208.0974, found 208.0969.

Desmethylstemoamide 13. To a solution of olefin **2** (52 mg, 80 μmol) in methanol (4 mL) was added 10% Pd–C (6 mg). The suspension was stirred overnight under H_2 atmosphere. The reaction was filtered through a small bed of Celite, and the solvent was evaporated to give desmethylstemoamide **13** (50 mg, 99%): R_f 0.26 (methanol–dichloromethane, 5:95); $[\alpha]_D^{25} = -144$ (*c* 1.0, CHCl_3); IR 2931, 1776, 1671, 1420, 1185 cm^{-1} ; ^1H NMR (CDCl_3) δ 4.29 (1H, dt, $J = 10.4, 3.0$ Hz), 4.15 (1H, dt, $J = 14.0, 2.1$ Hz), 4.00 (1H, dt, $J = 10.7, 6.6$ Hz), 2.92–2.80 (1H, m), 2.77–2.63 (1H, m), 2.65 (1H, dd, $J = 17.4, 8.5$ Hz), 2.46–2.36 (4H, m), 2.13–2.03 (1H, m), 1.90–1.84 (1H, m), 1.72 (1H, quin, $J = 10.7$ Hz), 1.62–1.52 (2H, m); ^{13}C NMR (CDCl_3) δ 174.9 (C), 174.2 (C), 80.0 (CH), 56.2 (CH), 45.1 (CH), 40.4 (CH_2), 34.8 (CH_2), 31.2 (CH_2), 30.7 (CH_2), 25.7 (CH_2), 22.8 (CH_2); *m/e* calcd for $\text{C}_{11}\text{H}_{16}\text{NO}_3$ 210.1130, found 210.1130.

(–)-Stemoamide 1. To a solution of desmethylstemoamide **13** (35 mg, 0.167 mmol) in anhydrous THF (1 mL) at -78°C was added 1 M LiHMDS solution in THF (0.3 mL). After 1 h, MeI (0.02 mL, 0.32 mmol) was added and stirring was continued for an additional 1 h. The reaction mixture was quenched with saturated ammonium chloride, extracted with ethyl acetate, dried over Na_2SO_4 , and concentrated in vacuo. The crude residue was purified by silica gel chromatography by eluting with dichloromethane/methanol (9.5:0.5) to give stemoamide (25 mg, 70%): $[\alpha]_D^{25} = -187$ (*c* 0.5, CH_3OH); mp = $185-186^\circ\text{C}$; ^1H NMR (CDCl_3) δ 4.21 (1H, dt, $J = 10.6, 3.0$ Hz), 4.16 (1H, m), 4.00 (1H, dt, $J = 10.8, 6.4$ Hz), 2.66 (1H, dd, $J = 14.3, 12.3$ Hz), 2.60 (1H, dq, $J = 12.5, 6.8$ Hz), 2.45–2.38 (4H, m), 2.09–1.84 (1H, m), 1.90–1.84 (1H, m), 1.72 (1H, quint, $J = 10.8$ Hz), 1.58–1.49 (2H, m), 1.31 (3H, d, $J = 6.9$ Hz); ^{13}C NMR (CDCl_3) δ 177.55 (C), 174.22 (C), 77.81 (CH), 56.01 (CH), 52.87 (CH), 40.41 (CH_2), 37.51 (CH), 34.99 (CH_2), 30.81 (CH_2), 25.80 (CH_2), 22.77 (CH_2), 14.30 (CH_3).

Acknowledgment. This research was supported by the National Science Foundation (CHE-0111292). We are indebted to Dr. Blake Watkins (University of Mississippi) for obtaining all the HRMS and to Dr. Dale Swenson for the X-ray crystallographic analysis of stemoamide.

Supporting Information Available: Copies of ^1H - and ^{13}C -spectra for selected compounds (**7**, **9–11**, and **1**) and ortep drawing and CIF file for the X-ray structure of (–)-stemoamide (**1**). This material is available free of charge via the Internet at <http://pubs.acs.org>.

JO052364L

Model studies on the ring construction of the auriside macrolactone

Rodolfo Tello-Aburto, Adrián Ochoa-Teran and Horacio F. Olivo*

Division of Medicinal and Natural Products Chemistry, The University of Iowa, Iowa City, IA 52242, United States

Received 19 May 2006; revised 5 June 2006; accepted 8 June 2006

Available online 30 June 2006

Abstract—The preparation of a 12-membered ring macrolactone model of auriside that contains a pendant diene chain bearing a bromide was investigated employing two approaches. The first approach utilized an oxidative rearrangement of a tertiary allylic alcohol on a 12-membered ring. The second approach was based on a 1,4-methylation of an ynone followed by macrolactonization. © 2006 Elsevier Ltd. All rights reserved.

Aurisides A and B are cytotoxic marine polyketides isolated from the Japanese sea hare *Dolabella auricularia* by Yamada and co-workers in 1996.¹ These two molecules exhibited significant cytotoxicity against HeLa S₃ cervical cancer cell lines. The aurisides are glycosylated 14-membered macrolactones, bridged through a hemiketal moiety, possessing a brominated conjugated diene side chain on C13, and bearing different rhamnose derived sugars on C5. Their unusual structure and significant cytotoxicity have attracted interest in their synthesis.^{2–4} We envisioned a highly convergent approach that involves building two fragments, the C1–C9 northern fragment possessing an aldehyde and an ester,⁵ and the C10–C17 southern fragment containing a brominated diene.⁶ Herein, we present our synthetic studies to assemble the C10–C17 fragment with a simple aldehyde in a 12-membered model macrolactone (Fig. 1).

We envisioned beginning the construction of the macrolactone with a bromodiene already in place. We examined two different strategies to combine and convert the C1–C9 and C10–C17 fragments into the desired model macrocycle, Figure 2. The first strategy relies on an oxidative rearrangement of a tertiary alcohol to furnish the desired α,β -unsaturated ketone **1** (path a). The second strategy focuses on a 1,4-alkylation to an ynone followed by macrolactonization (path b). These two strategies employ two similar C10–C17 fragments containing the conjugated bromodiene side chain **4** and **6**, both of them prepared from the versatile acyl imide

7.^{6,7} The tertiary alcohol **2** could be obtained by selective Grignard 1,2-addition to an enone, and the macrolactone could be prepared utilizing Yamaguchi's reagent. The propargylic ketone **5** could be accessed via addition of the acetylide of **6** to aldehyde **3** followed by oxidation of the resulting alcohol.

The oxidative tertiary allylic alcohol rearrangement strategy is illustrated in Figure 3. The synthesis starts from aldol product **7**,⁶ which was protected as the triethylsilyl ether. Chiral thiazolidinethione auxiliaries are easily displaced by several nucleophiles.^{7,8} The thiazolidinethione group of **8** was displaced with methyl (bis-methoxy)phosphonate and butyl lithium to furnish β -ketophosphonate **9** in excellent yield.⁹ Coupling of ketophosphonate **9** and aldehyde **3**¹⁰ was accomplished using barium hydroxide in THF in 85% yield.¹¹ Selective methylation of ketone **10** was carried out with excess methyl Grignard reagent at low temperature to afford **11** in 53% yield (75% based on recovered starting material). Concurrent desilylation of the TES group and ester hydrolysis of compound **11** occurred smoothly with lithium hydroxide and provided **12** in 88% yield. Formation of the 12-membered ring lactone **2** was accomplished using Yamaguchi's reagent in 81% yield.¹²

With tertiary allylic alcohol **2** in hand, we investigated appropriate conditions to carry out the desired oxidative rearrangement to α,β -unsaturated ketone **1**. A recent report showed that this rearrangement can be carried out effectively with five and six-membered cyclic tertiary alcohols to β -disubstituted α,β -unsaturated ketones using IBX in DMSO at 55 °C.¹³ Unfortunately, no product was observed in our more challenging 12-membered ring system using hypervalent iodine reagents.

* Corresponding author. Tel.: +1 319 335 8849; fax: +1 319 335 8766; e-mail: horacio-olivo@uiowa.edu

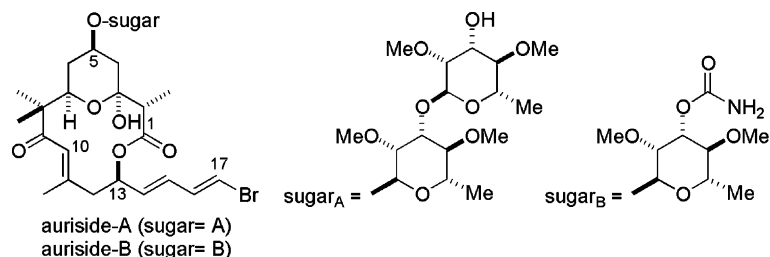


Figure 1. Aurisides A and B.

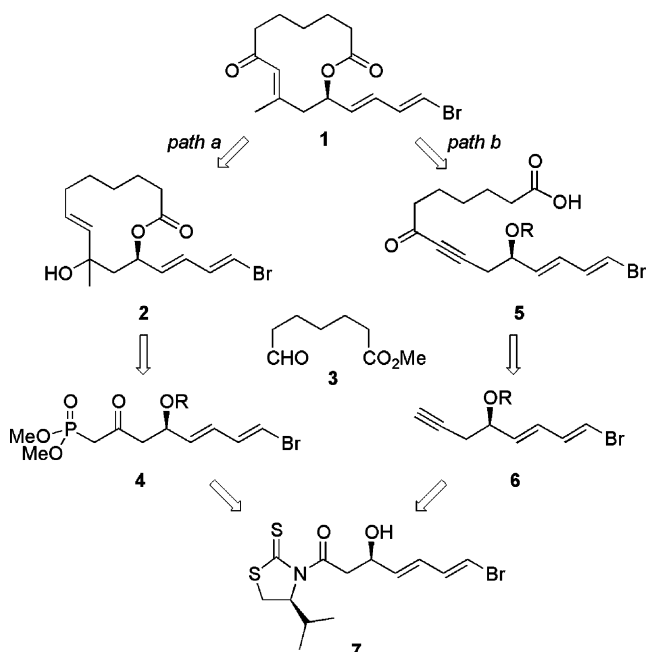


Figure 2. Strategies for the coupling of C1–C9 and C10–C17 fragments.

However, the desired product was formed as a single isomer using PCC and excess *p*-TsOH in CH₂Cl₂, albeit in low 30% yield and no starting material isolated.¹⁴ We believe the acidic conditions needed for the rearrangement might not be compatible with the allylic lactone present in the molecule, but no other product could be identified.

In our alternate strategy, ketone C9 is already in place, Figure 4. The thiazolidinethione aldol product **7** was

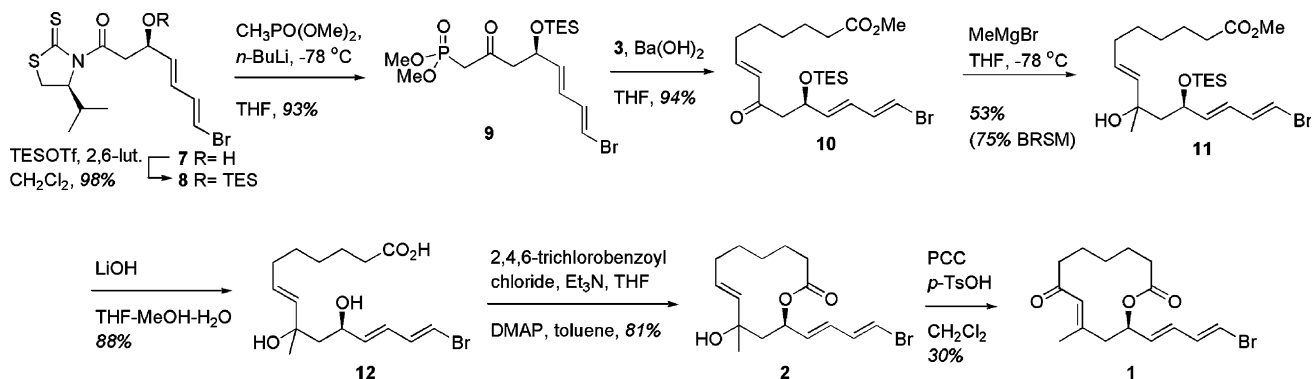


Figure 3. Oxidative tertiary allylic alcohol rearrangement.

protected with a TBS group. The thiazolidinethione **13** was reduced directly to aldehyde **14** using dibal-H at low temperature. Homologation of the aldehyde was accomplished with Ohira's reagent at low temperature to avoid β-elimination.⁶ Coupling of alkyne **15** with aldehyde **3** was accomplished with LDA at low temperature to give an inconsequential diastereomeric mixture of alcohols **16**. Compound **16** was subjected to hydrolysis, oxidation with Dess–Martin reagent, and addition of Gilman's reagent to the corresponding ynone.¹⁵ An inseparable mixture of isomeric enones **17-*E/Z*** was isolated in 74% yield. The ratio of isomers was determined by ¹H NMR and NOE experiments of the mixture (*E/Z*, 1.5:1). Cleavage of the silyl group was successful when TAS-F was added to **17** in wet DMF.^{16,17} Interestingly, we observed that the *E*-isomer **17** was deprotected faster than the more hindered *Z*-isomer. Thus, alcohol **18** was isolated uncontaminated from the *Z*-isomer. Yonemitsu's modification¹⁸ of the Yamaguchi's protocol gave the desired 12-membered lactone **1** in 45% yield.

The cyclization of compound **18** to build model macrolactone **1** occurred in modest yield (45%). Interestingly, macrolactonization of the seco-acid of the auriside aglycon by Paterson occurred cleanly in 86% yield.³

In summary, we have investigated two approaches to construct a model macrolactone ring that should be applied successfully to our synthesis of aurisides. The two approaches make use of an aldehyde (the northern fragment) and two similar C10–C17 fragments (southern fragment) that were prepared from a common aldol product. Although the two approaches present some problems, the 1,4-methyl-addition-macrolactonization seems to be a more appealing alternative, since the late-stage steps of the synthesis require mild conditions.

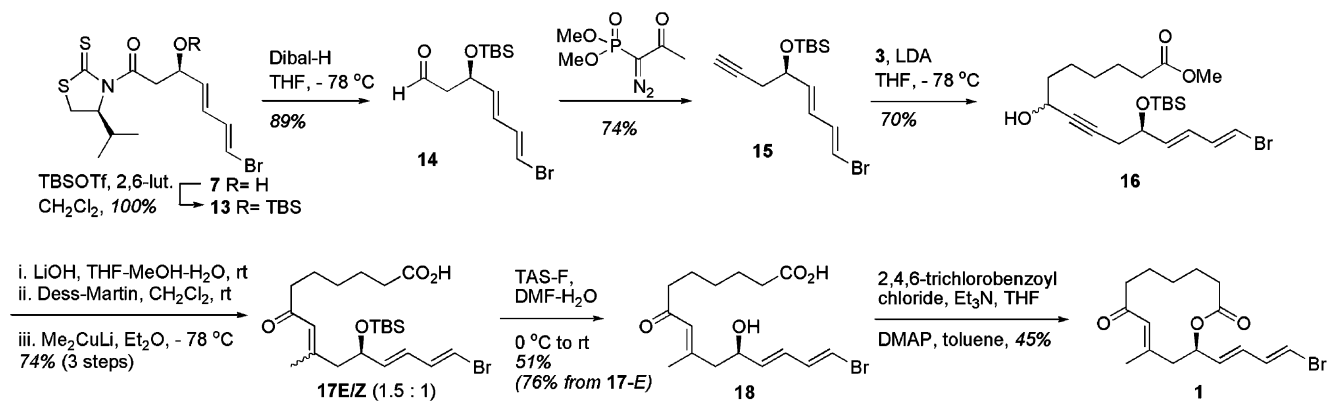


Figure 4. 1,4-Methyl addition—macrolactonization.

Current efforts in our laboratory are focused on applying this methodology to the total synthesis of the aurisides.

Acknowledgements

This work was supported by research grants from the National Science Foundation (CHE-0111292 and ECC-0310689).

Supplementary data

Copies of ^1H and ^{13}C NMR of compounds **1–3**, and **7–18**. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2006.06.041.

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