Tetrahedron Letters 52 (2011) 3379–3381

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

Synthetic study of yonarolide: stereoselective construction of the tricyclic core

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ARTICLE INFO

Article history:
Received 9 March 2011
Revised 21 April 2011
Accepted 22 April 2011
Available online 5 May 2011

Keywords:
Yonarolide
Diels–Alder reaction
Intramolecular aldol condensation
Tricyclic core
Retro-Michael–Michael addition

ABSTRACT

Stereoselective construction of the tricyclic core of yonarolide (**1**), a marine norditerpenoid, was achieved. This synthetic route includes a Diels–Alder reaction and an intramolecular aldol condensation. It also involves efficient epimerization through a retro-Michael reaction–Michael addition and will be applicable to the total synthesis of **1**.

1. Introduction

Soft coral of the genus *Sinuralia* has been a rich source of bioactive natural products, including various terpenoidal metabolites. Yonarolide (**1**), isolated in 1995 from the Okinawan soft coral of the genus *Sinuralia*, is a tetracyclic norditerpenoid.[1] The structure of yonarolide (**1**) was assigned based on 2D-NMR spectra, HSQC, HMBC, and ^{1}H–^{1}H COSY and NOESY analysis to be a tricyclo[7.5.0.0^{3,7}]tetradecane (named the yonarane skeleton) tethered to a γ-lactone ring (Fig. 1), which was unprecedented in natural products. The stereochemistry at the C11 position of the seven-membered ring in **1** has not been identified, and no pharmacologic effects have been reported for **1**. More recently, sinulochmodin C (**2**)[2] and scabrolide A (**3**)[3–6] and B (**4**)[3] have been identified as natural products isolated from soft corals of the genus *Sinuralia* that also possess the same yonarane skeleton. The structural features render **1** an ideal target for a total synthesis. To the best of our knowledge, there is no report to date of any synthetic study of these norditerpenoids possessing the yonarane skeleton. Herein we describe the stereoselective construction of the tricyclic lactone of yonarolide (**1**) based on an intramolecular aldol condensation as the first entry in the synthetic study of these natural products.

2. Results and discussion

Our strategy for the synthesis of the tricyclic lactone **5** is outlined in Scheme 1. The target compound **5** would be derived from the diketone derivative **6** by intramolecular aldol condensation. Compound **6** would be obtained by an intermolecular Diels–Alder reaction of the γ-lactone derivative **7** with the diene derivative **8** using a Lewis acid promoter.

The synthesis of the target molecule **5** was initiated with the construction of the dihydroisobenzofuran-1,5-dione framework via a Diels–Alder reaction. First, the γ-lactone derivative playing the role of the dienophile (compound **7**) was synthesized as shown in Scheme 2. Protection of the ketone group of commercially available **9** gave ethylene acetal **10** in excellent yield.[7] A one pot reaction involving reduction of the methyl ester moiety using DIBALH, followed by vinylation of the resultant aldehyde with

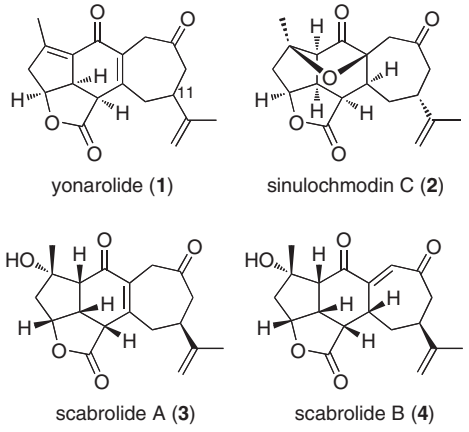

Figure 1. Structures of yonarolide (**1**) and related compounds.

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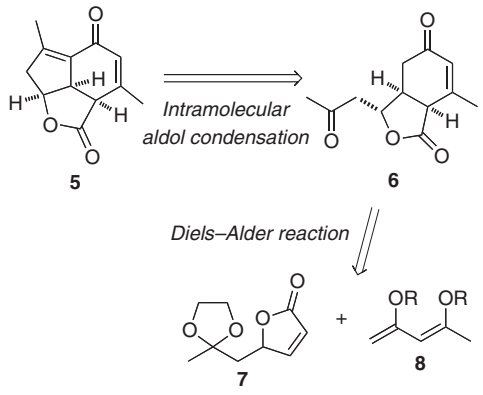
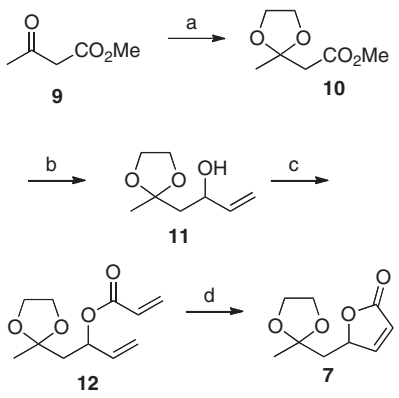
doi:10.1016/j.tetlet.2011.04.092



Scheme 1. Strategy for the synthesis of tricyclic core **5**.



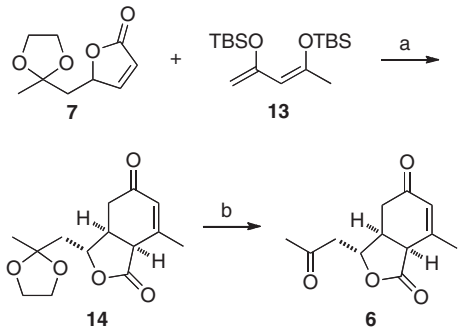
Scheme 2. Reagents and conditions: (a) ethyleneglycol, *p*-TsOH, toluene, reflux, 2 h, 91%; (b) DIBALH, toluene, −78 °C, 2 h → −50 °C, 0.5 h, then vinylmagnesium chloride, −78 → 0 °C, 0.5 h, 85%; (c) acryloyl chloride, Et_3N, CH_2Cl_2, 0 °C, 2 h, 85%; (d) Grubbs-2nd, toluene, 100 °C, 0.5 h, 99%.

vinylmagnesium chloride yielded allyl alcohol **11** (85%). After esterification of **11** with acryloyl chloride, ring closing metathesis of **12** using the Grubbs second generation catalyst produced the furanone derivative **7** in 84% over all yield.

With compound **7** in hand, construction of the dihydroisobenzofuran-1,5-dione framework via the Diels–Alder reaction between dienophile **7** and diene **13**[8] (readily prepared from acetylacetone) was studied as shown in Scheme 3. After several attempts (heated condition or combination of trifluoromethanesulfonamide and dimethylaluminum chloride[9]), use of a combination of trimethylaluminum and bis(trifluoromethanesulfonyl)methane[10] as the Lewis acid catalyst provided the best result, with the desired Diels–Alder adduct **14** obtained in 57% yield as a single diastereomer.[11] Treatment of **14** with *p*-TsOH in acetone led to cleavage of the acetal moiety in **14** to give the aldol condensation precursor diketone derivative **6** in good yield.

The structure of **14** was confirmed by NMR experiments as depicted in Figure 2, wherein clear NOE interactions between 3a-H and 7a-H, 3a-H and 4α-H, 3-H and 4β-H, and 3a-H and 1′-H, respectively, were observed. These results indicated that the stereochemical relationships between C3 and C3a and C3a and C7a in **14** were *anti* and *syn*, respectively.

With the stereoselective synthesis of the aldol condensation of precursor **6** achieved, our interest then turned to the next stage. The relative configuration at the C3 position in **6** was contrary to that of yonarolide (**1**). Additionally, construction of the tricyclic compound from **6** was expected to be excessively difficult because the two reaction points at the C4 position and the carbonyl group



Scheme 3. Reagents and conditions: (a) Tf_2CH_2, Me_3Al, $(CH_2Cl)_2$, rt, 1 h, 57%; (b) *p*-TsOH, acetone, 50 °C, 2 h, 92%.

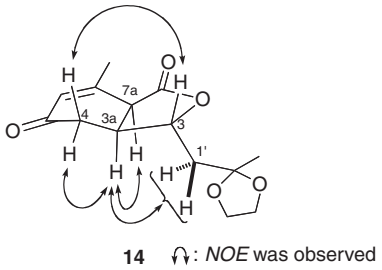


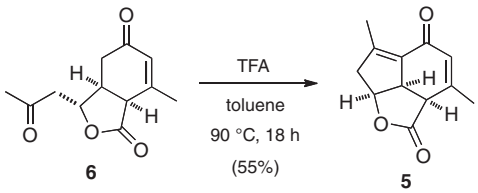
Figure 2. Selected NOE correlations for the Diels–Alder adduct **14**.

on the side chain in this configuration were far apart. It was necessary for construction of the target molecule **5** to reverse the stereochemistry of the C3 position before forming the cyclopentene unit via an aldol condensation. To execute this inversion at the C3 position, our proposed strategy involved a retro-Michael reaction–Michael addition sequence followed by a subsequent intramolecular aldol condensation under basic or acidic conditions.

Although synthesis of **5** from **6** under several basic conditions (*t*-BuOK, Et_3N, DBU, K_2CO_3) was unsuccessful,[12] treatment of **6** with trifluoroacetic acid[13] in toluene produced the desired compound **5**[14] in 55% yield in Scheme 4. The structure of **5** was assigned by NMR experiments as depicted in Figure 3.

Three observed key NOE interactions between 2a-H and 7b-H and 7a-H and 7b-H in the NOESY analysis of **5** disclosed that the stereochemical relationships between all of the bridgehead protons were each of the *syn* configuration, and these experimental facts revealed that the retro-Michael reaction–Michael addition–intramolecular aldol condensation proceeded smoothly under strong acidic conditions to afford the desired tricyclic lactone **5**, one of the core structures of yonarolide (**1**).

A proposed mechanism accounting for the construction of **5** is depicted in Scheme 5. Intramolecular aldol reaction of enol **17** generated from 3α-**6** to produce the tricyclic lactone **18** was not able to proceed, because the aldol reaction donor (the C4 carbon in the cyclic enol group) and the acceptor (the C2′ carbonyl group on the C3 side chain) are located too far away from each other in



Scheme 4. Construction of the tricyclic lactone **5** from **6**.

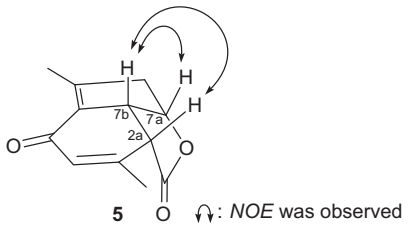
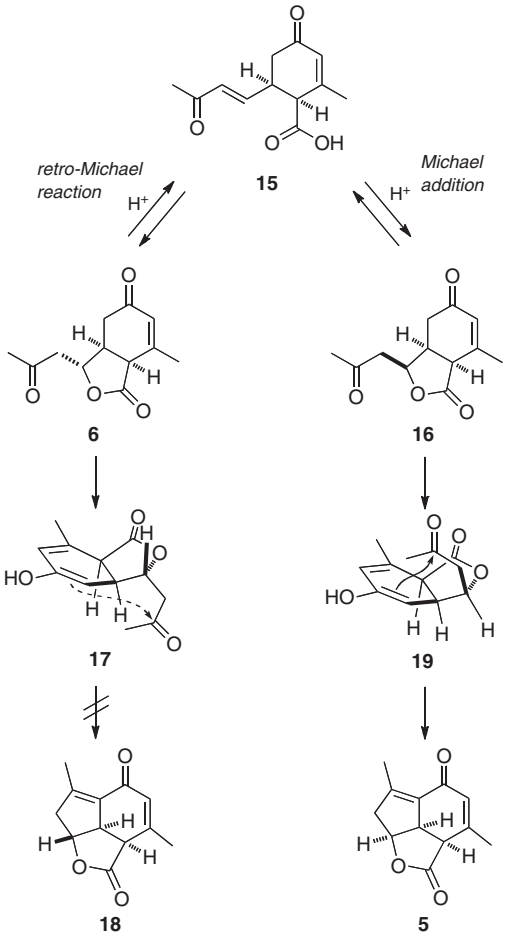


Figure 3. Selected NOE correlations of the tricyclic lactone **5**.



Scheme 5. Proposed mechanism for the construction of tricyclic lactone **5**.

enol **17**. On the other hand, the retro-Michael reaction of 3α-**6** and **6** leads to generation of enone **15**, which undergoes an intramolecular Michael addition reaction to produce compound **16**, which has the side chain at the β position. Compounds **6** and **15** and **15** and **16** are in equilibrium with one another. Consequently, epimerization at the C3 side chain results in the acceptor part gaining access to the donor part, and the intramolecular aldol reaction occurs in enol **19** (generated from **16**) to give the desired target tricyclic compound **5** as a single diastereoisomer.

In conclusion, the stereoselective construction of the tricyclic core of yonarolide (**1**) and related natural products (**2**–**4**) was accomplished from the methyl ester **9** in a total of eight steps and in 29% overall yield. This synthetic methodology involved the following features: (i) intermolecular Diels–Alder reaction between the furanone derivative **7** and diene **13**, (ii) intramolecular aldol condensation involving epimerization via a retro-Michael reaction–Michael addition. This concise synthetic methodology will be applicable to the total synthesis of yonarolide (**1**), a project that is now in progress in our laboratory.

Acknowledgments

This work was supported in part by a grant for private universities and a Grant-in-Aid for Scientific Research (C) (No. 21590024) from MEXT of Japan.

References and notes

1. Iguchi, K.; Kajiyama, K.; Yamada, Y. *Tetrahedron Lett.* **1995**, *36*, 8807–8808.
2. Tseng, Y.-J.; Ahmed, A. F.; Dai, C.-F.; Chiang, M. Y.; Sheu, J.-H. *Org. Lett.* **2005**, *7*, 3813–3816.
3. Sheu, J.-H.; Ahmed, A. F.; Shiue, R.-T.; Dai, C.-F.; Kuo, Y.-H. *J. Nat. Prod.* **2002**, *65*, 1904–1908.
4. Ahmed, A. F.; Shiue, R.-T.; Wang, G.-H.; Dai, C.-F.; Kuo, Y.-H.; Sheu, J.-H. *Tetrahedron* **2003**, *59*, 7337–7344.
5. Rudi, A.; Shmul, G.; Benayahu, Y.; Kashman, Y. *Tetrahedron Lett.* **2006**, *47*, 2937–2939.
6. Tseng, Y.-J.; Ahmed, A. F.; Hsu, C.-H.; Su, J.-H.; Dai, C.-F.; Sheu, J.-H. *J. Chin. Chem. Soc.* **2007**, *54*, 1041–1044.
7. (a) Boisse, T.; Rigo, B.; Millet, R.; Hénichart, J.-P. *Tetrahedron* **2007**, *63*, 10511–10520; (b) Cavallaro, R. A.; Filocamo, L.; Galuppi, A.; Galione, A.; Brufani, M.; Genazzani, A. A. *J. Med. Chem.* **1999**, *42*, 2527–2534.
8. (a) Ward, D. E.; Shen, J. *Org. Lett.* **2007**, *9*, 2843–2846; (b) Denmark, S. E.; Heemstra, J. R., Jr. *J. Org. Chem.* **2007**, *72*, 5668–5688.
9. Saito, A.; Ito, H.; Taguchi, T. *Org. Lett.* **2002**, *4*, 4619–4621.
10. (a) Yanai, H.; Takahashi, A.; Taguchi, T. *Tetrahedron* **2007**, *63*, 12149–12159; (b) Yanai, H.; Takahashi, A.; Taguchi, T. *Tetrahedron Lett.* **2007**, *48*, 2993–2997.
11. *Experimental procedures*. Preparation of **14**. To a solution of bis(trifluoro methanesulfonyl)methane (183 mg, 0.65 mmol) in dichloroethane (3 mL) was added dropwise trimethylaluminum (1.03 M in hexane solution, 0.82 mL, 0.85 mmol) at room temperature under argon. After stirring for 0.5 h, this mixture was added to a solution of **7** (200 mg, 1.09 mmol) and **13** (535 mg, 1.63 mmol) in dichloroethane (3 mL), and the reaction mixture stirred at room temperature for 0.5 h. The reaction mixture was then quenched with aqueous 1 M HCl, extracted three times with $CHCl_3$. The combined organic layers were washed with brine, dried over $MgSO_4$ and the solvent removed. The residue was purified by flash column chromatography (hexane–AcOEt, 1:1) to afford **14** (495 mg, 57%) as white crystals. IR (KBr) 2988, 2912, 1774, 1730, 1671 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.31 (3H, s), 1.95 (1H, dd, J = 14.9, 5.0 Hz), 2.03 (1H, dd, J = 14.9, 6.3 Hz), 2.12 (3H, s), 2.40 (2H, dd, J = 16.9, 7.0 Hz), 2.93 (1H, quint, J = 6.7 Hz), 3.36 (1H, d, J = 3.8 Hz), 3.83–3.98 (4H, m), 4.31 (1H, q, J = 6.0 Hz), 6.00 (1H, br s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 22.3, 24.3, 35.8, 40.0, 42.2, 44.5, 64.5, 64.6, 79.5, 107.8, 128.4, 152.3, 172.5, 195.4; HRMS (ESI–TOF) calcd for $C_{14}H_{19}O_5$ [$(M+H)^+$] 267.1232, found 267.1245.
12. Treatment of **5** with several bases gave the aromatic compound along with a complex mixture. This aromatization reaction likely results from a slower reaction rate for the Michael addition of the unsaturated ketone on the side chain resulting from the retro-Michael reaction versus the reaction rate for the formation of the conjugated enol ether via deprotonation at the γ position (C3) in the retro-Michael product.
13. Use of acetic acid instead of trifluoroacetic acid gave trace amount of **5** along with a complex mixture including the enone **15**.
14. *Spectral data for (2aR*,7aR*,7bS*)-3,6-dimethyl-7,7a-dihydroindeno[1,7-bc]furan-2,5(2aH,7bH)-dione* **5**. Colorless needles; mp 125–127 °C (from hexane–AcOEt); IR (KBr) 2935, 1754, 1655 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 2.08 (3H, br s), 2.23 (3H, d, J = 1.1 Hz), 2.73 (1H, d, J = 19.0 Hz), 2.96 (1H, ddquint, J = 19.0, 4.4, 1.6 Hz), 3.38 (1H, d, J = 8.2 Hz), 3.95–4.06 (1H, m), 5.03 (1H, t, J = 4.6 Hz), 6.00 (1H, quint, J = 1.3 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 15.4, 23.5, 45.5, 46.0, 51.0, 80.9, 127.4, 130.1, 148.9, 152.3, 172.3, 185.7; HRMS (ESI–TOF) calcd for $C_{12}H_{13}O_3$ [$(M+H)^+$] 205.0865, found 205.087.