Tetrahedron Letters 50 (2009) 3191–3194

Contents lists available at ScienceDirect

Tetrahedron Letters

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

A synthetic study on gymnastatins F and Q: the tandem Michael and aldol reaction approach

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ARTICLE INFO

Article history:
Received 5 December 2008
Revised 21 January 2009
Accepted 27 January 2009
Available online 5 February 2009

Keywords:
Marine natural product
Gymnastatin
Bicyclo[3.3.1]nonane
Gymnascella dankaliensis

ABSTRACT

Gymnastatins F (**1**) and Q (**2**) were successfully synthesized using the tandem Michael and aldol reaction of the corresponding spirodienones with hemiacetal functions. Inspection of the optical purities of the substrates suggested that undesired racemization does not proceed during the tandem reaction. Results of theoretical calculations agreed with the ratio of the reaction outcome.

Gymnastatins, isolated from the fungus *Gymnascella dankaliensis* OUPS-N134 which was obtained from the sponge *Halichondria japonica*, are members of the marine spiroisoxazoline family,[1,2] and their chlorine-containing structure is rather exceptional, compared with other congeners such as aerothionin[3] and aeroplysinin-1[4] possessing bromine atoms. In addition to the typical spirodienone structure, gymnastatins F (**1**)[1] and Q (**2**)[2] share the bicyclo[3.3.1]nonane framework, which might be produced biosynthetically by the tandem Michael and aldol reaction of gymnastatin A (**3**).[3,4] These compounds exhibit inhibitory activity against the murine P388 cell line.[1,2] As part of our ongoing investigation on this class of natural products,[5] we have accomplished total synthesis of gymnastatin A (**3**) employing anodic oxidation.[6–9] Preliminary antimicrobial assay of **3** and its synthetic intermediates revealed moderate to good inhibition against Gram-positive including MRSA, -negative bacteria, fungi, and *Mycobacterium*.[6] As the bicyclo[3.3.1]nonane congeners were expected to exhibit remarkable biological activities, a biomimetic construction of gymnastatins F (**1**) and Q (**2**) was carried out, starting from the corresponding spirodienone derivatives (see Fig. 1).

Synthesis of model bicyclic compounds **5** *and* **6**: The cyclization reactions were examined extensively, and the desired biomimetic reaction was shown to proceed under the basic conditions (Table 1). The model substrate **4**[6] provided the bicyclic products **5** and **6**, and their stereochemistry was determined by ^{1}H NMR techniques involving the NOE experiments (Fig. 2). Their epimeric relationship suggested that **5** and **6** may be produced by the initial attack of a MeO group controlled by the interaction with the *tert*-hydroxyl moiety of the substrate, followed by nucleophilic attack of an anion generated at the carbon possessing a chlorine atom to the aldehyde function. Consequently, in all of the entries, both **5** and **6** were produced in moderate to good yields. The latter **6** showed preferential yield as compared with the former, with the exception of the PhSH cases (entries 12 and 13), which showed slight preference for the production of **5**. The reason for this reverse selection is unclear, although the benzene ring may modulate a transition state conformation. Upon use of thioalkoxide (over 2 mol equiv), the corresponding thio derivatives were produced under the aprotic solvent conditions (entries 10, 11), whereas **5** (R = OMe) and **6** (R = OMe) were produced under the MeOH conditions (entries 8 and 9). Upon exposure of **5** or **6** to the basic conditions, a plausible retroaldol reaction provided a mixture of **5** and **6.** This observation indicated that **5** and **6** may be produced by thermodynamic control under the tandem reaction conditions.

Synthesis of **1** *and* **2**: As the expected cyclization was achieved by the model compound **4**, application of this reaction to gymnastatin A (**3**) carrying the entire carbon framework of **1** and **2** was attempted. Although the best condition for **4** (entry 7 in Table 1) did not function, reaction of **3** with a slight excess of KOH in MeOH (10 mM, 0 °C, overnight) produced **1** in very low yield, and **2** was not obtained, probably due to repulsion between the fatty acid group and the cyclohexenone moiety. Disturbance of the acid moiety in the cyclization prompted us to examine the two-step procedure involving cyclization of the *N*-Boc derivative **7**,[6] followed by attachment of the acid moiety.

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doi:10.1016/j.tetlet.2009.01.156

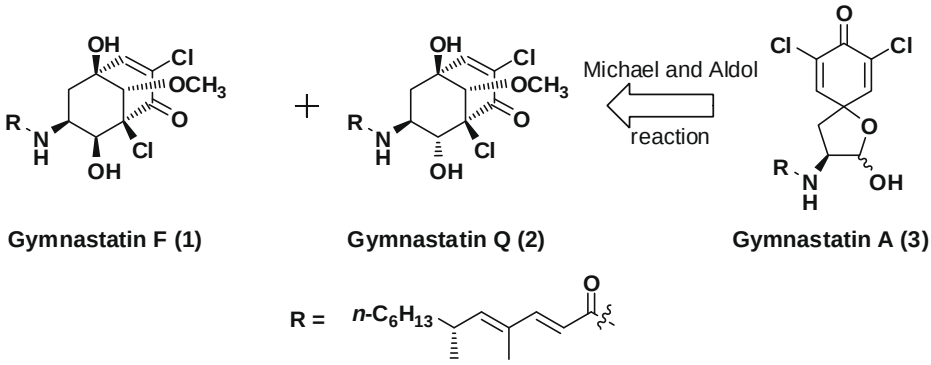
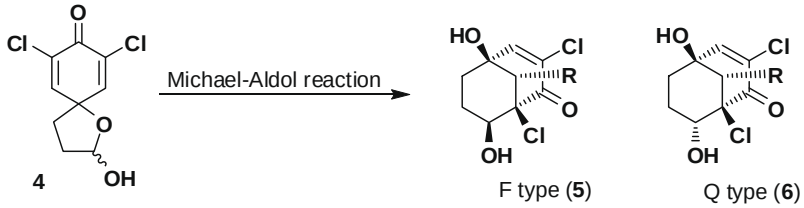


Figure 1. Gymnastatins.

Table 1
The Michael-aldol reaction of **4** leading to the corresponding bicyclo[3.3.1]nonanes (**5**, **6**)



Entries	Conditions	R	Yields (%)	
			5	**6**
1	K_2CO_3, MeOH	OMe	27	29
2	K_2CO_3 (0.1 mol equiv), MeOH		22	30
3	NaOMe, MeOH		29	34
4	LiOH, MeOH		25	37
5	NaOH, MeOH		22	36
6	KOH, MeOH		30	35
7	KOH, MeOH, 18-crown-6		36	64
8	NaSMe, MeOH		36	56
9	NaSEt, MeOH		32	44
10	NaSMe, THF	SMe	25	33
11	NaSEt, THF	SEt	18	42
12	PhSH, KOH, MeOH	SPh	32	23
13	PhSH, KOH, MeOH, 18-crown-6		47	35

After several attempts, the hemiacetal **7** was submitted to the KOH/MeOH conditions to give the corresponding bicyclic derivatives **8** and a mixture of **9** and **10**, among four possible isomers (Scheme 1). Although the latter mixture could not be differentiated in the *N*-Boc form, the following derivatization to introduce the fatty acid **12** revealed a 3:1 ratio of **2** (type-**9**) and unnatural **13** (type-**10**). Inspection of **8** by HPLC analysis (DAICEL CHIRALCEL OJ-H column, solvent: hexane/EtOH = 90:10, 0.5 mL/min) indicated 88% ee of optical purity.[10] In addition, the optical purity of the acetyl derivative of **7**,[11] which was a precursor of **8** and **9**, was 88% ee by HPLC analysis (DAICEL CHIRALCEL AS-H column, solvent: hexane/EtOH = 85:15, 0.5 mL/min). We considered racemization to reduce their optical purity to take place at the aldehyde or dienone precursor of **7**. Accordingly, the tandem Michael and aldol reaction did not involve the racemization.

To explain the observed ratio of products, density functional calculations were carried out. There are four possible isomers (**8**, **9**, **10,** and **11**) as product of the tandem reaction of **7**. The structures and relative energy values of both products and the transition states leading to each product are summarized in Figure 3. The ob-

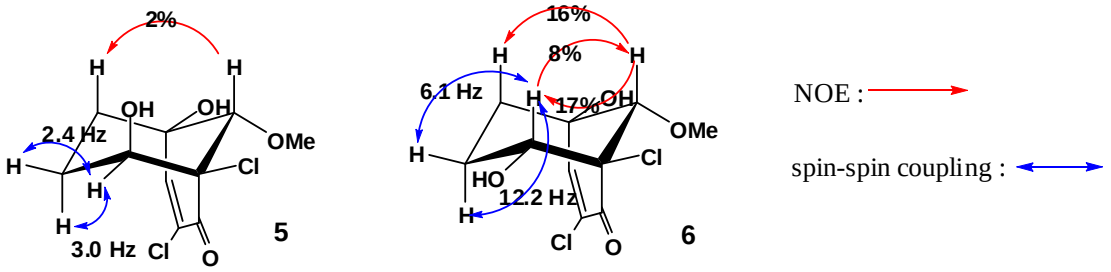
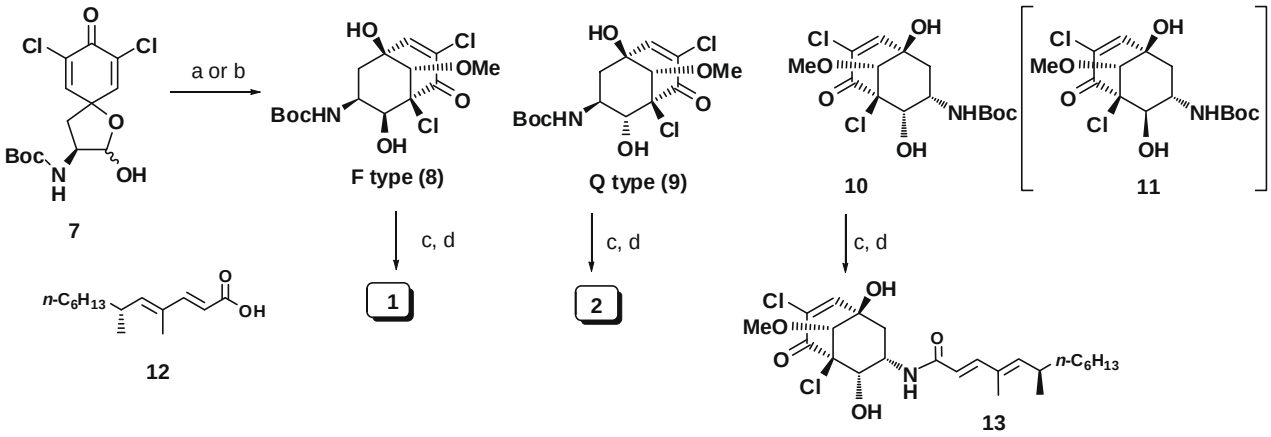


Figure 2. NOE correlations and spin-spin couplings of **5** and **6**.



Scheme 1. Reaction conditions: (a) KOH, MeOH, −20 → 0 °C (**8**, 15%; **9** + **10**, 18%); (b) KOH, 18-crown-6, MeOH, −20 → 0 °C (**8**, 17%; **9** + **10**, 35%); (c) TFA, CH_2Cl_2, room temp.; (d) **12**, EDCI, DMAP, Et_3N, (**1**, 37% in 2 steps), (81% as a 3:1 mixture of **2** and **13** in 2 steps).

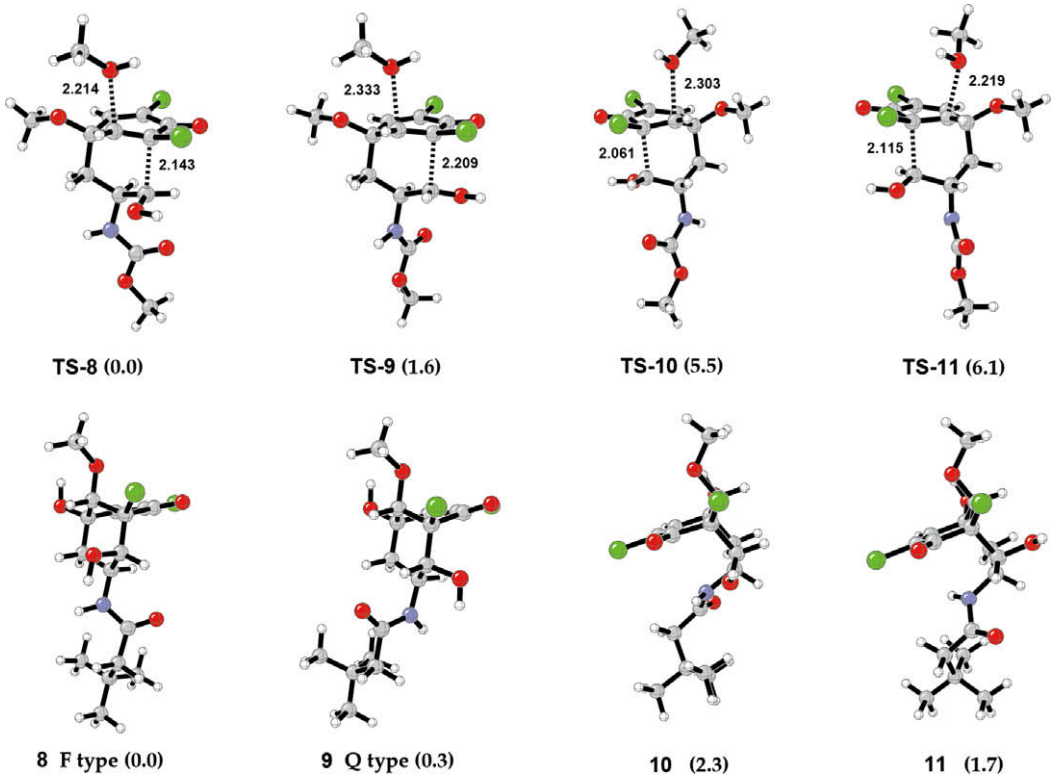


Figure 3. Structures of transition states (above) and products (below) of the Michael-aldol reactions of **4** obtained at B3LYP/6-31G(d,p) level. Distances of forming/breaking bonds in transition structures are shown in Å. Numbers in parenthesis are relative energies within transition states (relative to **TS-8**) and products (relative to **8**), in kcal/mol.

served product ratio is best explained if we consider that the reaction is controlled thermodynamically, that is, the product ratio is governed by the relative stability of the products. Although there is no good explanation why we did not obtain **11**, relative energy of activation for **10** and **11** is considerably high (5.5 and 6.1 kcal/mol from **8**, respectively), compared with that for **8**, and it is possible that the production of **10** and **11** is hindered by kinetic manner. All the calculations were carried out at B3LYP/6-31G(d,p) level using GAUSSIAN03[12] and GAMESS[13] program packages. PCM solvation model was used for the products, with the dielectric constant of methanol (32.6). Transition states are modeled as protonated forms, since the attempt to obtain corresponding transition states in anionic form could not provide sensible structures. The cationic model may not be ideal, considering that the experimental condition is basic. Nevertheless, we consider that the computational results should reflect the relative stability of the transition states at certain extent (see Fig. 4).

As mentioned above, acid hydrolysis followed by coupling with the carboxylic acid **12** yielded **1**[1,2] and a 3:1 mixture of **2**[1,2] and **13**. To obtain optically pure samples, the synthetic samples were submitted to chromatographic separation by recycling preparative HPLC [**1**: JAIGEL-1H column ($CHCl_3$, 3.5 mL/min); **2** and **13**: a connection of JAIGEL-1H and JAIGEL-2H ($CHCl_3$, 3.8 mL/min)] to give the corresponding products: **1**, $[\alpha]_D^{20}$ −71.5 (*c* 0.16, $CHCl_3$), **2**, $[\alpha]_D^{20}$ −71.8 (*c* 0.50, $CHCl_3$) [lit. data **1**, −77.7 (*c* 0.16, $CHCl_3$),[1] **2**, −34.3 (*c* 0.26, $CHCl_3$)[2]].[14] As can be seen, while optical rotation of syn-

thetic gymnastatin F (**1**) was in accordance with the reported data, optical rotation of natural gymnastatin Q (**2**) was smaller than that of the synthetic sample. Although we could not determine whether the observed difference in optical rotation is due to a mixture of enantiomers or impurities, our optically pure samples will be subjected to biological assessment.

In conclusion, a biomimetic approach to gymnastatins F (**1**) and Q (**2**) was executed using the Michael-aldol reaction protocol, which was initiated by the selective introduction of OMe and SR groups to C-7 positions. Further inspection of their biological activities is currently in progress.

Acknowledgments

This work was supported by High-Tech Research Center Project for Private Universities matching fund subsidy from MEXT, 2006-2011. The authors are grateful to Professor Atsushi Numata, Osaka University of Pharmaceutical Science, and Professor Hideo Kigoshi, University of Tsukuba, for helpful discussions and technical assistance. Part of the computations was performed using Research Center for Computational Science, Okazaki, Japan.

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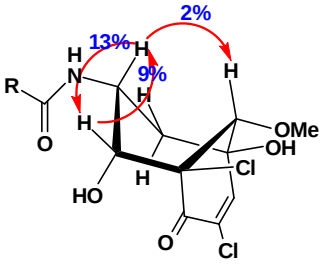

Figure 4. NOE correlations of **13**.