Pergamon

Tetrahedron Letters 43 (2002) 7773–7775

TETRAHEDRON LETTERS

Total synthesis and absolute configuration of marine *bisnor*-diterpenoid elisabethin C

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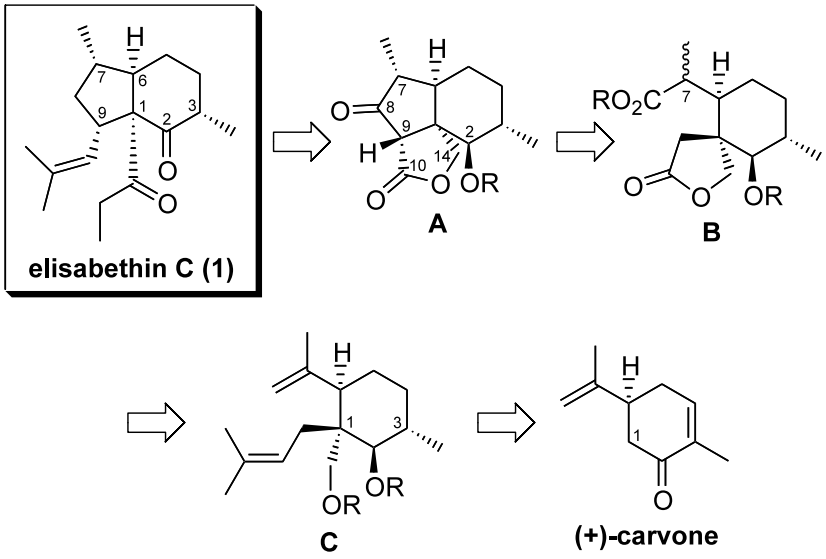
Received 22 July 2002; revised 19 August 2002; accepted 23 August 2002

Abstract—Total synthesis of marine *bisnor*-diterpenoid elisabethin C was successfully carried out by stereoselective construction of bicyclo[4.3.0]nonane ring system with Dieckmann cyclization as the key step. The absolute configuration of elisabethin C was determined based on this total synthesis.

Elisabethin C (**1**) is a novel *bisnor*-diterpenoid which was isolated from the gorgonian *Pseudopterogorgia elisabethae*, obtained off San Andrés Island, Colombia, by Rodríguez in 1998.[1] Its structure is characterized by a unique bicyclic carbon skeleton (*bisnorseco*-elisabethane skeleton); its relative configuration was determined by NOESY though the absolute configuration remains to be elucidated. Elisabethin C (**1**) was found to have antituberculosis activity against *Mycobacterium tuberculosis* H37Rv (42% inhibition) at 12.5 μg/mL. Thus, its unique structure and biological activity prompted the authors to undertake the total synthesis of elisabethin C. The total synthesis of elisabethin C is presented here for the first time, along with determination of its absolute configuration.

The synthesis of elisabethin C (**1**) involves stereoselective construction of the bicyclo[4.3.0]nonane ring system in the Dieckmann cyclization as a key step, as shown in Scheme 1. The authors used the key intermediate **A**, which undergoes transformation to elisabethin C (**1**) via deoxygenation at C-8[2] position and elongation



Scheme 1. Retrosynthetic analysis of elisabethin C (**1**).

Keywords: biologically active compounds; marine metabolites; terpenes and terpenoids.

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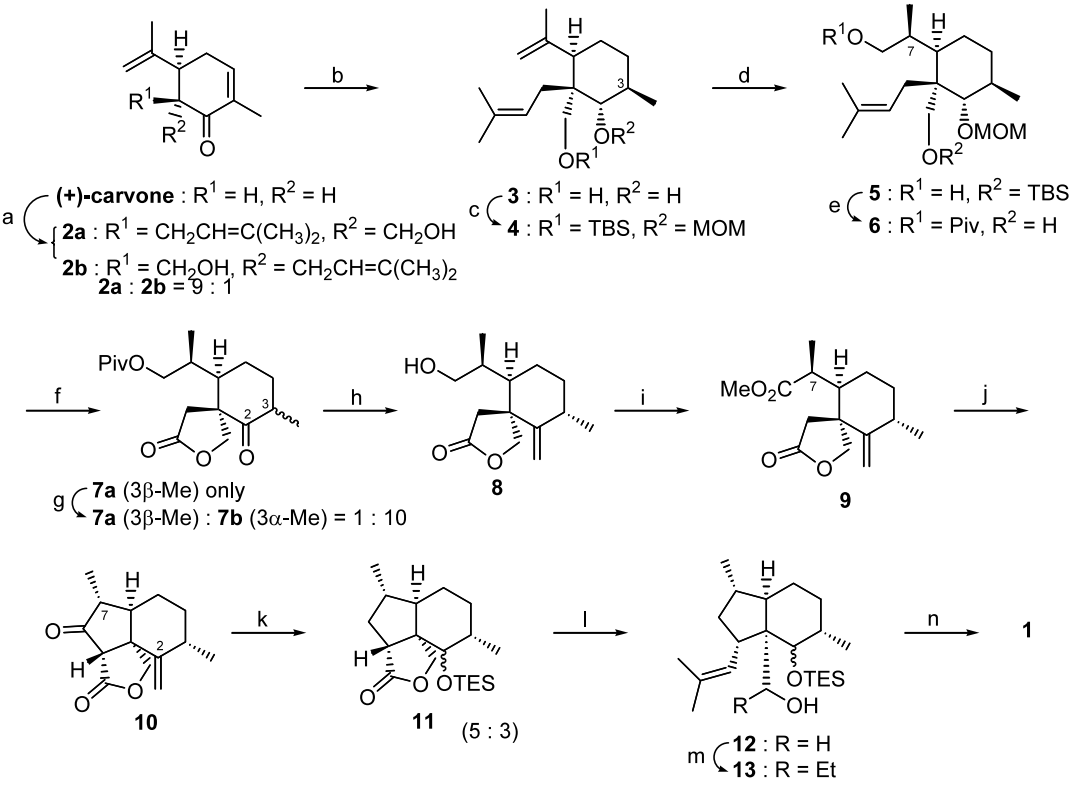
0040-4039/02/$ - see front matter
PII: S0040-4039(02)01831-2

of carbon chains at C-10 and C-14 positions. Ketolactone **A** is likely produced via Dieckmann cyclization of ester lactone **B**. Ester lactone **B** can be obtained from compound **C** via construction of lactone and hydroboration. Compound **C** can be prepared from commercially available (+)-carvone through stereocontrolled alkylation at C-1 position and stereocontrolled reduction of enone.

The synthesis of elisabethin C (**1**) was initiated using (+)-carvone (Scheme 2). Lithium enolate of (+)-carvone was treated with prenyl bromide to give a mono-prenylated compound, the subsequent treatment of which with LDA in THF and then a solution of formaldehyde in THF provided a diastereomeric mixture of alcohols **2a** and **2b** (**2a**:**2b**=9:1).[3] Alcohols **2a** and **2b** were separated and alcohol **2a** was reduced with Na in liquid NH_3 in the presence of EtOH to give diol **3** as the sole product.[4] The methyl group at C-3 in diol **3** was found to have β-configuration, thus being opposite that of natural elisabethin C. The isomerization of the methyl group at C-3 was consequently carried out in a later step. The primary hydroxy group in diol **3** was protected as TBS ether and the secondary hydroxy group as MOM ether to give compound **4**. Regio- and stereoselective hydroboration of compound **4** using 9-BBN[5] afforded alcohol **5** as the sole product.[6] The hydroxy group in **5** was protected as a pivaloyl group and the TBS group was removed by treatment with TBAF to afford alcohol **6**, which then underwent conversion to ketolactone **7a** by following four steps: (1) ozonolysis of prenyl group; (2) PDC oxidation of hemiacetal; (3) removal of MOM group and (4) PCC oxidation of secondary hydroxy group. Ketolactone **7a** was treated with K_2CO_3 in MeOH at 40°C to give a mixture of ketolactone **7a** and **7b** (**7a**:**7b**=1:10)[7] and following the separation of which, the carbonyl group in **7b** was protected as *exo*-methylene by treatment with $TMSCH_2Li$ and then 5N HCl.[8] Removal of the pivaloyl group with NaOMe gave alcohol **8**. Esterification of carboxylic acid obtained by oxidation of primary alcohol **8** using MeI and K_2CO_3 in acetone afforded ester **9**. Ester lactone **9** was treated with NaH in the presence of 15-crown-5 to give ketolactone **10** as the sole product[9] by Dieckmann cyclization[10] followed by isomerization of the methyl group at C-7. The relative configuration



Scheme 2. *Reagents and conditions*: (a) (1) LDA, THF, −42°C, then $(CH_3)_2C{=}CHCH_2Br$, −42°C to rt, 89%, (2) LDA, THF, −78°C, then HCHO, −78°C, 84%; (b) Na, liq. NH_3, EtOH, −78°C, 70%; (c) (1) TBSCl, imidazole, DMF, rt, (2) MOMCl, $^iPr_2NEt$, CH_2ClCH_2Cl, 50°C, 97% (two steps); (d) 9-BBN, THF, rt, then NaOH, H_2O_2, 92%; (e) (1) PivCl, pyridine, 0°C, (2) TBAF, THF, 50°C, 97% (two steps); (f) (1) O_3, $NaHCO_3$, MeOH, −78°C, then Me_2S, −78°C to rt, (2) PDC, 4 Å MS, CH_2Cl_2, rt, 92% (two steps), (3) 1N HCl, THF, rt, 99%, (4) PCC, 4 Å MS, CH_2Cl_2, rt, 99%; (g) K_2CO_3, MeOH, 40°C, 98%; (h) (1) $TMSCH_2Li$, THF, −78°C, then 5N HCl, rt, (2) NaOMe, MeOH, 50°C, then 1N HCl, 92% (two steps); (i) (1) Jones reagent, acetone, 0°C, (2) K_2CO_3, MeI, acetone, rt, 80% (two steps); (j) NaH, 15-crown-5, benzene, reflux, 84%; (k) (1) $NaBH_4$, MeOH, −42°C, 90%, (2) NaH, CS_2, MeI, THF, 0°C to rt, 81%, (3) $^nBu_3SnH$, Et_3B, toluene, 0°C, 67%, (4) O_3, $NaHCO_3$, MeOH, −78°C, then $NaBH_4$, −78°C to rt, (5) TESOTf, 2,6-lutidine, CH_2Cl_2, 0°C, 84% (two steps); (l) (1) DIBAH, toluene, −78°C, (2) $Ph_3P^+CH(CH_3)_2I^-$, PhLi, toluene, rt, 78% (two steps); (m) (1) Dess–Martin periodinane, $NaHCO_3$, CH_2Cl_2, rt, 99%, (2) EtMgBr, THF, rt, 67%; (n) (1) TBAF, THF, rt, 99%, (2) Dess–Martin periodinane, $NaHCO_3$, CH_2Cl_2, rt, quant.

of the methyl group at C-7 in ketolactone **10** was regulated to the α-configuration through control of thermodynamic factors. Deoxygenation[11] at C-8 position in **10** was carried out as follows: (1) $NaBH_4$ reduction to give secondary alcohol; (2) treatment with NaH, CS_2, MeI to give xanthate and (3) radical reduction with $^nBu_3SnH$. *exo*-Methylene at C-2 was ozonated followed by $NaBH_4$ reduction to give a secondary alcohol, whose secondary hydroxy group was protected using TESOTf and 2,6-lutidine to give TES ether **11** as a diastereomeric mixture (5:3). This mixture was used in the following reaction without separation. Lactone **11** reduced to hemiacetal using DIBAH was subjected to the Wittig reaction[12] to afford alcohol **12**. The oxidation of alcohol **12** with Dess–Martin periodinane[13] gave aldehyde and which, by treatment with EtMgBr, gave alcohol **13** and reductive product **12**. Removal of TES group in compound **13** gave diol. Finally, oxidation of the two secondary hydroxy groups with Dess–Martin periodinane provided elisabethin C (**1**), $[\alpha]_D^{25}$ −33.3° (*c* 0.3, $CHCl_3$). Spectral data and the sign of optical rotation of synthesized elisabethin C (**1**) were identical with those of natural elisabethin C, $[\alpha]_D^{25}$ −31.2° (*c* 0.5, $CHCl_3$).[1] Thus, the absolute configuration of elisabethin C is clearly shown to be **1** by the present synthesis.

Acknowledgements

This work was supported in part by a Grant-in-Aid for Scientific Research from Ministry of Education, Culture, Sports, Science and Technology of Japan.

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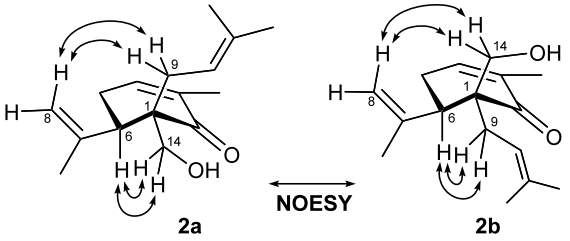
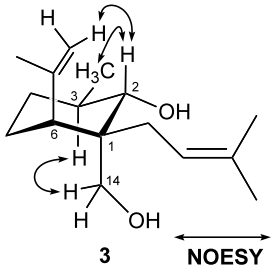
2. Numbering of all compounds in this paper is in accordance with that for elisabethin C.
3. The relative configuration of alcohols **2a** and **2b** was determined by their NOESY spectra, respectively.



2a **2b**

4. The relative configuration of diol **3** was determined by its NOESY spectrum.



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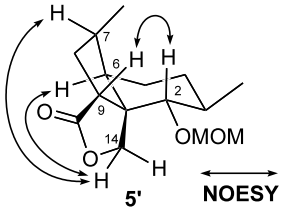
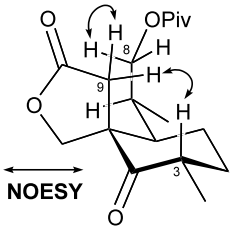
6. The relative configuration of methyl group at C-7 in alcohol **5** was determined by NOESY spectrum of lactone **5′** which was prepared from alcohol **5** by following seven steps: (1) PivCl, pyridine, 0°C; (2) TBAF, THF, 50°C, 97% (two steps); (3) O_3, $NaHCO_3$, MeOH, −78°C, then Me_2S, −78°C to rt; (4) PDC, 4 Å MS, CH_2Cl_2, rt, 92% (two steps); (5) NaOMe, MeOH, 50°C, 94%; (6) TsCl, pyridine, 0°C, 99% and (7) ^{t}BuOK, THF, 0°C, 92%.



5′

7. The relative configuration of ketolactone **7b** was confirmed by its NOESY spectrum.



7b

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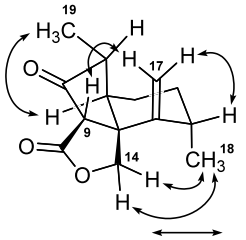

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