Pergamon

Tetrahedron Letters 42 (2001) 2801–2803

TETRAHEDRON LETTERS

Synthesis and structure determination of *iso*-cladospolide B†

Xavier Franck, Maria E. Vaz Araujo, Jean-Christophe Jullian, Reynald Hocquemiller and Bruno Figadère*

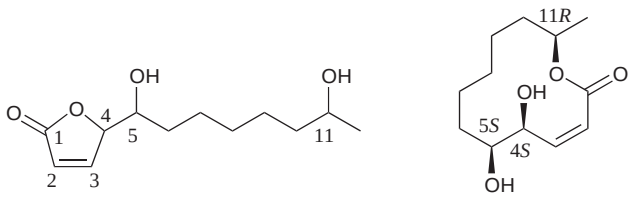
Laboratoire de Pharmacognosie, associé au CNRS (BIOCIS), Université Paris-Sud, Faculté de Pharmacie, rue Jean-Baptiste Clément, 92296 Châtenay-Malabry, France

Received 9 February 2001; revised 12 February 2001; accepted 22 February 2001

Abstract—*iso*-Cladospolide B **1** was previously characterized from the fungal isolate I96S215 obtained from a marine sponge collected in Indonesia. However, neither the relative nor the absolute configurations were reported. We describe in this letter a synthetic pathway which allowed us to prepare **1** and attribute the absolute configurations of the three stereogenic centers.

Terrestrial, as well as marine fungi, are an extremely rich source of pharmaceutically interesting compounds of various structures. Recently from a sponge collected in Indonesia, Ireland obtained, from the fermentation of the fungal isolate I96S215, several hexaketides.[1] Among those new compounds, *iso*-cladospolide B **1** showed a butenolide moiety substituted at the γ position by an aliphatic chain bearing two hydroxyl groups. Although neither the relative nor the absolute configurations of the three stereogenic centers of **1** was known, its close relationship with the fully characterized natural product cladospolide B **2**[2] prompted us to synthesize **1** (Fig. 1).

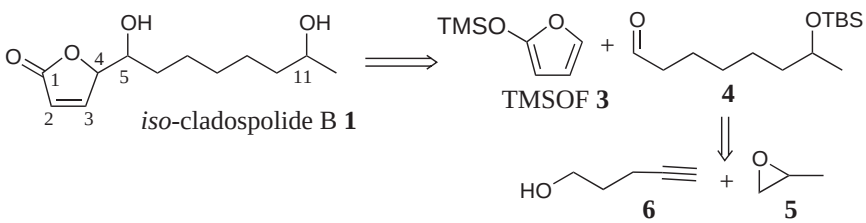
The retrosynthetic scheme shows that the key step relies on the use of the asymmetric vinyloguous Mukaiyama aldol reaction[3] between 2-trimethylsilyloxyfuran **3** (TMSOF) and the desired aldehyde **4**. The latter could be obtained in a few steps from the commercially available starting materials propylene oxide **5** and pent-4-yn-1-ol **6** (Fig. 2). Both enantiomers of propylene oxide **5** are available, but the *R* isomer was used in order to prepare the 11-*R* isomers of **1** (the use of the *S* isomer would give rise to the complementary stereoisomers of **1**).



iso-cladospolide B **1** cladospolide B **2**

Figure 1.

Pent-4-yn-1-ol **6** was protected as a benzyl ether[4] by treatment with sodium hydride and benzyl bromide in THF in the presence of 0.1 equiv of Bu_4NBr to afford



iso-cladospolide B **1** TMSOF **3** **4** **6** **5**

Figure 2.

Keywords: polyketides; marine fungi; asymmetric aldol reaction; structure determination.

* Corresponding author. Fax: (33) 1 46 83 53 99; e-mail: bruno.figadere@cep.u-psud.fr

† Dedicated to Professor W. H. Okamura on the occasion of his 60th birthday.

PII: S0040-4039(01)00323-9

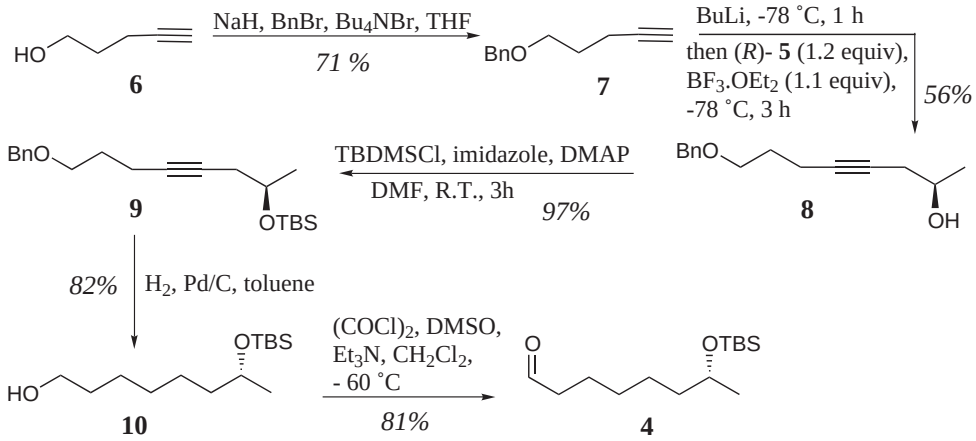


Figure 3.

7 in 71% yield. Then metallation of the latter with *n*-butyllithium at −78°C in THF[5] followed by additions of (*R*)-propylene oxide **5** and $BF_3{\cdot}OEt_2$, led to the homopropargyl alcohol **8** in 56% yield. We then decided to protect the secondary hydroxyl group of **8** as a hindered silyl ether by usual treatment[6] (TBDMSCl and imidazole in the presence of a catalytic amount of DMAP in DMF, to afford **9** in 97% yield), to avoid competitive interactions of this hydroxyl with the catalyst during the aldolization step. Then, treatment of **9** in toluene under a hydrogen, atmosphere in the presence of palladium on charcoal[7] (Fig. 3), allowed us to simultaneously reduce the triple bond and deprotect the benzyl ether to give the desired saturated and deprotected primary alcohol **10** in 82% yield. It is noteworthy that the silyl ether remained unchanged during the hydrogenation step.[8] Finally, Swern oxidation[9] of **10** led to the desired aldehyde **4** in 81% yield.

Aldehyde **4** was then treated at −78°C in CH_2Cl_2 by TMSOF **3** in the presence of $BF_3{\cdot}OEt_2$ to afford a mixture of *erythro* **12a**,**13a**/*threo* **12b**,**13b** compounds (*erythro*/*threo* ratio = 15:85) in 60% yield (Fig. 4). The relative stereochemistry at C-4 and C-5 can be deduced from the ^1H and ^{13}C NMR data (see Table 1). For instance, ^1H chemical shifts of CH-3, CH-4 and CH-5 in **1** ($\delta_{CH\text{-}3}$ 7.63, $\delta_{CH\text{-}4}$ 5.07 and $\delta_{CH\text{-}5}$ 3.77 ppm) are in good agreement with the chemical shifts of CH-3, CH-4 and CH-5 in **12b**/**13b** ($\delta_{CH\text{-}3}$ 7.63, $\delta_{CH\text{-}4}$ 5.07 and $\delta_{CH\text{-}5}$ 3.78 ppm), and related compounds.[10] Furthermore comparison of the coupling constants for the CH-4 signals (td, $J = 4.9$ and 1.7 Hz for *erythro* and quin. $J = 1.8$ Hz for *threo* compounds) confirms the *threo* relative configuration for the natural product **1**.

^1H NMR analysis in $CDCl_3$ of this mixture in the presence of $Eu(hfc)_3$ showed that, not surprisingly, each diastereomer was in fact a 1:1 mixture of two *pseudo*-enantiomers **12a**/**13a** and **12b**/**13b**, the remote stereogenic center of **4** at C-11 (*iso*-cladospolide B numbering) being too far away from the reactive site to induce some selectivity in the aldolization reaction. The aldol reaction was thus performed under asymmetric catalysis through a stepwise addition:[3,10] the chiral catalyst was first prepared in Et_2O at room temperature by mixing $Ti(OiPr)_4$ (20 mol%) and either (*S*)- or (*R*)-Binol (40 mol%) for 1 h (method B or C, respectively), then the temperature was brought to −20°C and TMSOF **3** with aldehyde **4** added in four portions over a 6 h period of time. Mixtures of compounds were thus obtained in both cases which after deprotection (HF, in THF at rt for 12 h) afforded the products **12a**,**b** and

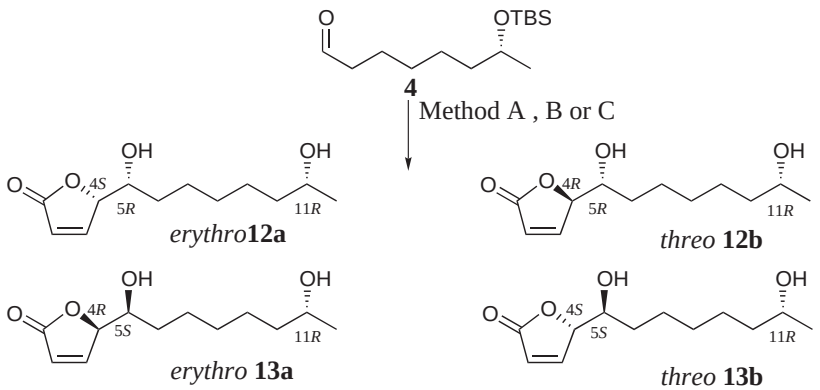


Figure 4. Method A: (1) TMSOF **3**, CH_2Cl_2, −78°C, $BF_3{\cdot}OEt_2$; (2) HF, THF; 60%. Method B: (1) TMSOF **3**, Et_2O, −20°C, $Ti(OiPr)_4$ (20%), (*S*)-Binol (40%); (2) HF, THF; 50%. Method C: (1) TMSOF **3**, Et_2O, −20°C, $Ti(OiPr)_4$ (20%), (*R*)-Binol (40%); (2) HF, THF; 50%.

Table 1. CD_3OD ^1H and ^{13}C NMR data[a] of **1** (500 MHz),[1] and synthetic **12a**/**13a** and **12b**/**13b** (400 MHz)

Atom	**1**	**12a**/**13a** (*erythro*)	**12b**/**13b** (*threo*)
1	– (175.75)	– (175.58)	– (175.78)
2	6.16 [dd, 5.8, 2.0] (122.71)	6.18 [dd, 7.0, 2.0] (122.95)	6.16 [dd, 5.8, 2.0] (122.69)
3	7.63 [dd, 5.8, 1.4] (157.13)	7.72 [dd, 5.8, 1.5] (156.56)	7.63 [dd, 5.8, 1.5] (157.11)
4	5.07 [quint., 1.8] (88.22)	5.01 [td, 4.9, 1.7] (88.37)	5.07 [quint., 1.8] (88.19)
5	3.77 (71.65)	3.70 (72.28)	3.78 (71.73)
6	1.56[b] (34.22)	1.56[b] (34.19)	1.56[b] (34.19)
7	1.36[b] (30.61[b])	1.37[b] (30.59[b])	1.36[b] (30.59[b])
8	1.35[b] (26.78[b])	1.37[b] (26.75[b])	1.36[b] (26.75[b])
9	1.56[b] (26.78[b])	1.56[b] (26.75[b])	1.56[b] (26.75[b])
10	1.42 (40.12)	1.42 (40.09)	1.42 (40.09)
11	3.70 (68.54)	3.70 (68.51)	3.70 (68.51)
12	1.13 [d, 6.2] (23.50)	1.13 [d, 6.2] (23.50)	1.13 [d, 6.2] (23.50)

[a] δ ppm [mult., J (Hz)] (^{13}C NMR).
[b] Assignments may be interchanged.

13a,**b** in around 50% combined yield which were analyzed by ^1H NMR in $CDCl_3$ in the presence of $Eu(hfc)_3$. It is noteworthy that the *pseudo*-enantiomers **12a** and **13a** or **12b** and **13b** were not separable by usual chromatography.

The diastereomeric ratio in experiment B was in favor of the *threo* isomers (d.r. = 65:35) which showed furthermore a **12b**/**13b** ratio of 85:15, whereas *erythro* isomers showed a **12a**/**13a** ratio of 75:25 (by ^1H NMR analysis in $CDCl_3$ in the presence of $Eu(hfc)_3$). However, in experiment C the *threo* and *erythro* isomers were obtained in a 50:50 ratio. In that case, the *threo* isomers showed a **12b**/**13b** ratio of 20:80, whereas *erythro* isomers showed a **12a**/**13a** ratio of 30:70.

Absolute configurations of the products drawn on Fig. 4, were deduced from comparison of the ^1H chemical shifts in the presence of $Eu(hfc)_3$ with those of related compounds.[10] Then specific rotations were measured in methanol after isolation by flash chromatographies of four *erythro* and *threo* enriched mixtures: $\mathbf{12a_{maj}}$, $[\alpha]_D = -32$ (*c* 0.66); $\mathbf{13a_{maj}}$, $[\alpha]_D = +15$ (*c* 0.55); $\mathbf{12b_{maj}}$, $[\alpha]_D = +54$ (*c* 0.45); $\mathbf{13b_{maj}}$, $[\alpha]_D = -47$ (*c* 0.75). After calculations,[11] comparison of the specific rotations with those of natural products (**1**, $[\alpha]_D = -90$;[1] **2**, $[\alpha]_D = +45$[2b]) did not unfortunately allow us to determine unambigously all absolute configurations of stereogenic centers of **1**. However, due to the strong influence of the butenolide moiety on the specific rotation, we can assume that **1** has the 4*S*,5*S* configuration, identical to cladospolide B **2**.

In conclusion, the synthesis of *iso*-cladospolide B **1** was performed in seven steps and 13% overall yield. The NMR data of the synthetic compounds, as well as the comparison of the specific rotations allow us to propose the absolute configuration of **1** as follows: 4*S*,5*S* and 11*R*, for close analogy with cladospolide B **2**. ^1H NMR analysis of the Mosher esters[12] of natural **1** would allow one to conclude without ambiguity on the absolute configuration at C-11.

Acknowledgements

We thank Professor C. M. Ireland for copies of NMR data of *iso*-cladospolide B and cladospolide B. M.E.V.A. thanks the University of Vigo for a SOCRATES fellowship.

References

1. Cameron, J. S.; Abbanat, D.; Bernan, V. S.; Maiese, W. M.; Greenstein, M.; Jompa, J.; Tahir, A.; Ireland, C. M. *J. Nat. Prod.* **2000**, *63*, 142–145.
2. (a) Hirota, A.; Sakai, H.; Isogai, A. *Agric. Biol. Chem.* **1985**, *49*, 731–735; (b) Fuji, Y.; Fukuda, A.; Hamasaki, T.; Ichimoto, I.; Nakajima, H. *Phytochemistry* **1995**, *40*, 1443–1446.
3. Szlosek, M.; Franck, X.; Figadère, B.; Cavé, A. *J. Org. Chem.* **1998**, *63*, 5169–5172.
4. Czernecki, S.; Georgoulis, C.; Provelenghiou, C. *Tetrahedron Lett.* **1976**, 3535.
5. Yamagushi, M.; Hirao, I. *Tetrahedron Lett.* **1983**, *24*, 391–394.
6. Corey, E. J.; Venkateswarlu, A. *J. Am. Chem. Soc.* **1972**, *94*, 6190.
7. Heathcock, C. H.; Ratcliffe, R. *J. Am. Chem. Soc.* **1971**, *93*, 1746.
8. Hattori, K.; Sajiki, H.; Hirota, K. *Tetrahedron Lett.* **2000**, *41*, 5711–5714.
9. Mancuso, A. J.; Swern, D. *Synthesis* **1981**, 165–185.
10. Szlosek, M.; Figadère, B. *Angew. Chem., Int. Ed.* **2000**, *39*, 1799–1801.
11. After calculations: **12a**, $[\alpha]_D = -152$; **13a**, $[\alpha]_D = +157$; **12b**, $[\alpha]_D = +99$; **13b**, $[\alpha]_D = -105$.
12. (a) Dale, J. A.; Mosher, H. S. *J. Am. Chem. Soc.* **1968**, *90*, 3732–3738; (b) Trost, B. M.; Belletire, J. L.; Godleski, S.; McDougal, M. C.; Balkovec, J. M. *J. Org. Chem.* **1986**, *51*, 2370–2374; (c) Duret, P.; Waechter, A. I.; Figadère, B.; Hocquemiller, R.; Cavé, A. *J. Org. Chem.* **1998**, *63*, 4717–4720.