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Synthesis of (−)- and (+)-hyrtiosal and their C-16 epimers

Inês Lunardi,[a] Gilvandete M. P. Santiago[b] and Paulo M. Imamura[a,*]

[a]*Instituto de Química, Universidade Estadual de Campinas, CEP 13.083-970, Campinas, São Paulo, Brazil*
[b]*Departamento de Farmácia, UFC, Ceará, Brazil*

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Abstract—A total synthesis of the marine sponge metabolite (−)-hyrtiosal along with its enantiomer (+)-hyrtiosal and their C-16 epimers were achieved starting from 30% ee copalic acid.

Marine sponges are a rich source of new marine natural products and the majority of compounds are reported focusing on biomimetical or ecological importance.[1] Many biologically active metabolites are terpenoids and (−)-hyrtiosal (**1**) is an example of sesterterpenoid isolated from the Okinawan marine sponge *Hyrtios erectus* which showed a potent cytotoxic activity against KB cell in vitro.[2] Its structure was elucidated spectroscopically and by chemical reactions and consists of a novel rearranged tricarbocyclic skeleton named hyrtiosane. The absolute configuration of the natural product was recently established by total synthesis.[3]

Here we report the synthesis of (−)-hyrtiosal (**1**), (+)-hyrtiosal (**2**) and their C-16 epimers, starting from 30% ee copalic acid (**3**)[4] (Fig. 1).

Isocopalenol (**4**), synthesized previously from **3** in three steps,[5] was mesylated in pyridine to give **5** in 95% yield (Scheme 1). The reaction of **5** with sodium cyanide in the presence of Adogen 464®,[6] gave nitrile **6** in 70% yield along with an elimination product (ca. 20%). Reduction of **6** with DIBAL in toluene, gave aldehyde **7** in good yield (87%). Treatment of **7** with 3-bromofuran and *n*-BuLi gives a (1.2:1) mixture of epimeric alcohols **8** (48.5%) and **9** (40.5%) that was separated by silica gel column chromatography. Since the purity of the starting copalic acid (**3**) was ~30% ee, esterification of **8** and **9** with (*S*)-*O*-methyl mandelic acid seems to be suitable for resolution and determination of the stereogenic center at C-16.[7] Thus, treatment of **8** with (*S*)-*O*-methyl mandelic acid in the presence of DCC and DMAP furnished two diastereoisomeric esters **10** (52%) and **11** (28%), easily separated by column chromatography (Scheme 2). Using the same sequence, **9** furnished compounds **12** (54%) and **13** (29%), separated by HPLC. Thus, the stereochemistry at C-16 of 4 stereoisomers could be established as shown in Scheme 2, according to Trost's model.[7]

Epoxidation of **11** with *m*CPBA at −40°C furnished **14** in 70% yield and subsequent rearrangement of the epoxide with $BF_3{\cdot}Et_2O$ at −23°C in nitromethane gave **15** in 78% yield (Scheme 3). Finally, hydrolysis of ester (*S*)-*O*-methyl mandelate was performed with K_2CO_3 in MeOH:THF:H_2O (1:1:0.5) to give (−)-hyrtiosal (**1**) $\{[\alpha]_D^{20} = -72.1°$ (*c* 0.59, $CHCl_3)\}$ in 66% yield. Literature[2,3] $\{[\alpha]_D^{20} = -73.8°$ (*c* 0.42, $CHCl_3)\}$ and $\{[\alpha]_D^{20} = -62.2°$ (*c* 0.74, $CHCl_3)\}$, respectively.

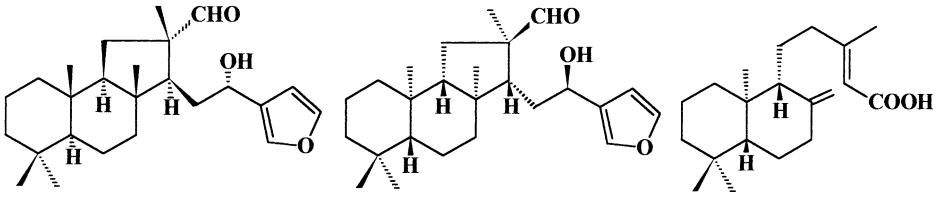

Figure 1.

Keywords: (+)-hyrtiosal; (−)-hyrtiosal; sesterterpene; copalic acid.

* Corresponding author. Fax: 55-19-37883023; e-mail: imam@iqm.unicamp.br

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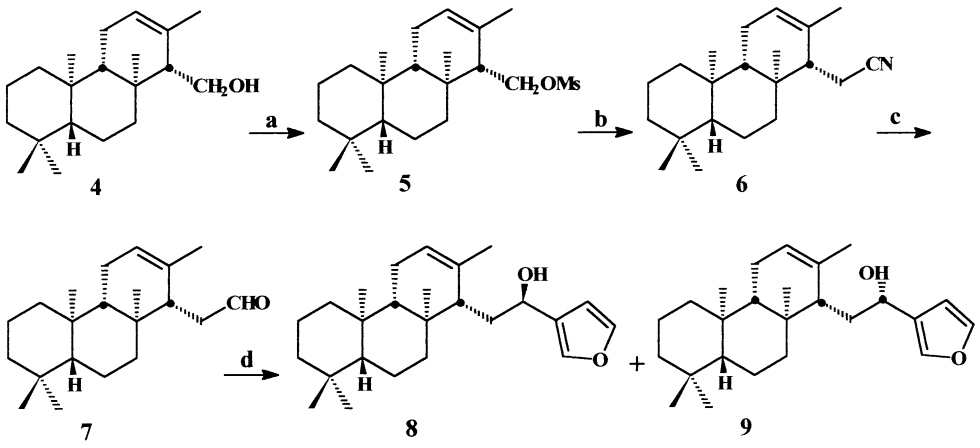
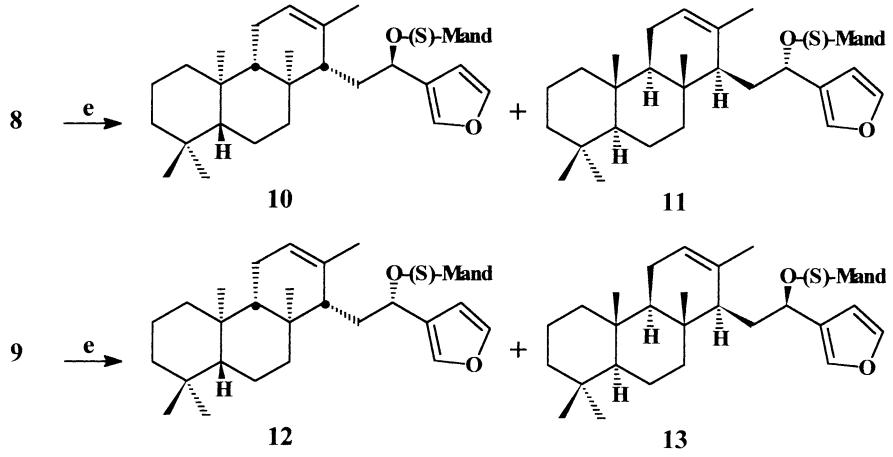
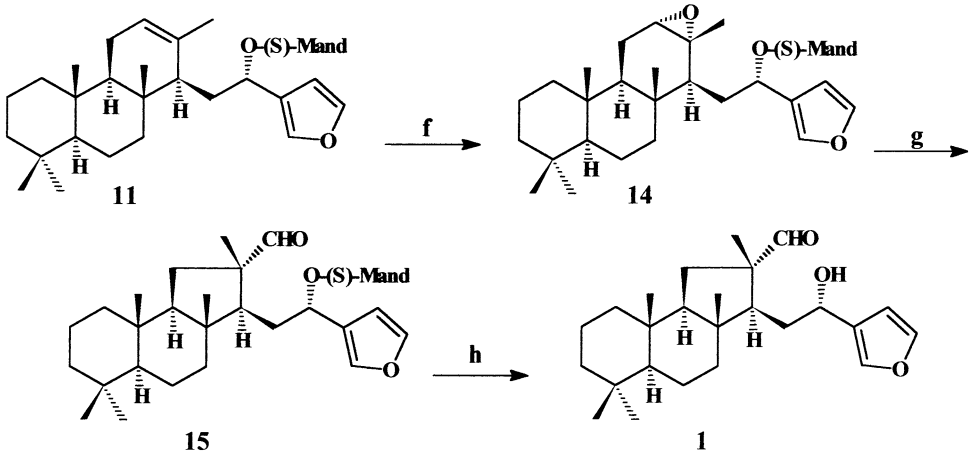


Scheme 1. *Reagents, conditions and yields*: (a) MsCl, pyridine, rt, 15 h, 95%; (b) NaCN, Adogen 464®, toluene:H_2O (10:1), 60°C, 36 h, 70%; (c) DIBAL, toluene, 0°C, 1.5 h, 87%; (d) *n*-BuLi/3-bromofuran/THF, −78°C, 1.5 h, **8** (48.5%) and **9** (40.5%)



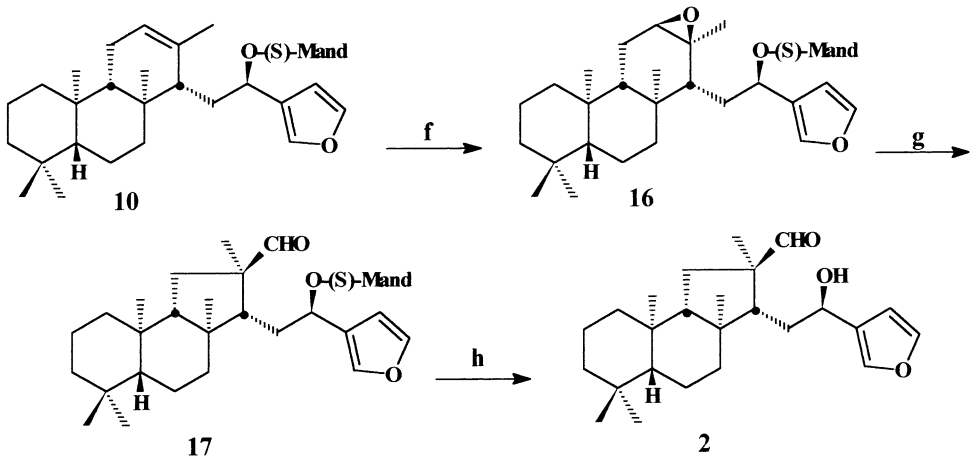
Scheme 2. *Reagents, conditions and yields*: (e) (*S*)-(+)-*O*-methyl mandelic acid, DCC, DMAP, CH_2Cl_2, rt, 2 h, **10** (52%), **11** (28%), **12** (54%) and **13** (29%).



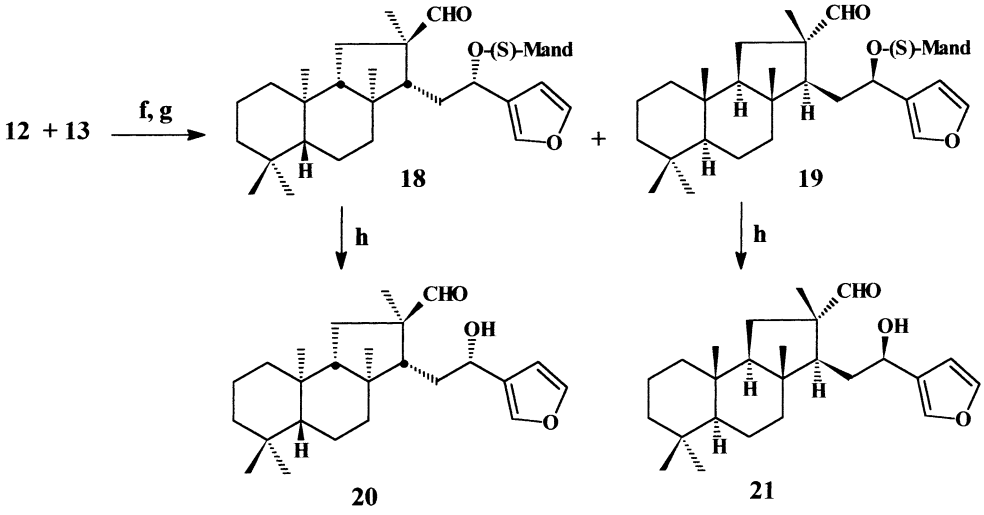
Scheme 3. *Reagents, conditions and yields*: (f) *m*CPBA, CH_2Cl_2, −40°C, 1.5 h, 70%; (g) $BF_3{\cdot}Et_2O$, CH_3NO_2, −23°C, 40 min, 78%; (h) K_2CO_3, MeOH:THF:H_2O (1:1:0.5), rt, 16 h, 66%.

Following the same sequence for the synthesis of **1** from **11**, compound **10** gave, after epoxidation, rearrangement of epoxide and hydrolysis of ester (*S*)-*O*-methyl mandelate, (+)-hyrtiosal (**2**) $\{[\alpha]_D^{20} = +64.2°$ (*c* 0.53, $CHCl_3)\}$ in 31% yield for three steps (Scheme 4).

In another sequence, although the separation of **12** and **13** could be performed at this stage, the mixture was epoxidized and submitted to the acidic rearrangements to give the aldehydes **18** and **19**, which were promptly separated by HPLC (Scheme 5).



Scheme 4. *Reagents, conditions and yields*: (f) *m*CPBA, CH_2Cl_2, –40°C, 1.5 h, 71%; (g) $BF_3{\cdot}Et_2O$, CH_3NO_2, –23°C, 1 h, 67%; (h) K_2CO_3, MeOH:THF:H_2O (1:1:0.5), rt, 16 h, 66%.



Scheme 5. *Reagents, conditions and yields*: (f) *m*CPBA, CH_2Cl_2, –40°C, 1.5 h, 88%; (g) $BF_3{\cdot}Et_2O$, CH_3NO_2, –23°C, 1 h, **18** (49.5%), **19** (33.5%); (h) K_2CO_3, MeOH:THF:H_2O (1:1:0.5), rt, 16 h, **20** (69%), **21** (75%).

Finally, the hydrolysis of esters **18** and **19**, separately, furnished compounds **20** (69%) and **21** (75%), respectively, the corresponding C-16 epimers of **2** and **1**. In summary, starting from 30% ee copalic acid, we completed the syntheses of (–)-hyrtiosal, (+)-hyrtiosal and their C-16 epimers.

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