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Novel and General Entry into Pseudoguaianolides. Formal and Enantioselective Synthesis of (+)-Confertin

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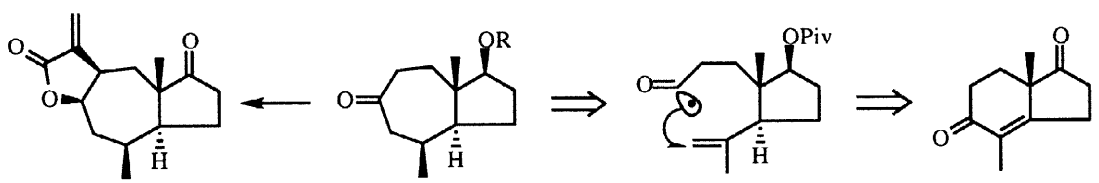
Abstract

A novel and general access to pseudoguaianolide sesquiterpenoids has been developed by employing a diastereoselective acyl radical-mediated 7-*endo-trigonal* mode of cyclization as a key reaction step. The methodology has successfully been applied to the formal enantioselective synthesis of (+)-confertin.

Keywords: Radicals and radical reactions; Terpene and terpenoids; Enantiocontrol

Pseudoguaianolides are a class of sesquiterpenoids found in a number of plant species and some members have attracted considerable attention because of their cytotoxic and antitumor activity [1]. Confertin (**1**), a representative of this class of sesquiterpenoids, was isolated from *Ambrosia confertiflora and A. tenuifolia* [2], and several total syntheses of it have been reported so far. However, most of them were racemic syntheses [3] and only two examples of enantioselective synthesis of the natural enantiomer (+)-**1** have been reported [4]. In this paper, we present a novel and general strategy for the construction of optically pure pseudoguaianolides by illustrating an enantiocontrolled formal synthesis of (+)-**1**. The key feature of our strategy is the combined use of a quaternary carbon construction methodology [5] using 5-*exo-trigonal* silylmethyl radical cyclization [6] and a highly diastereoselective 7-*endo-trigonal* cyclization (**3**→**2b**) of the acyl radical (**3**) [7], which would be derived from the optically active perhydroindenone (**4**) [8]. (Scheme 1)



1 **2a** R=TBS **2b** R=Piv **3** **4**

Scheme 1

The pivalate (**6**), prepared from the optically pure **4** {$[\alpha]_D$+250 (lit.[8][$\alpha]_D$+250)} via **5**, was reduced diastereoselectively with $NaBH_4$ in the presence of $CeCl_3$ to the allylic alcohol (**7**), which was silylated with

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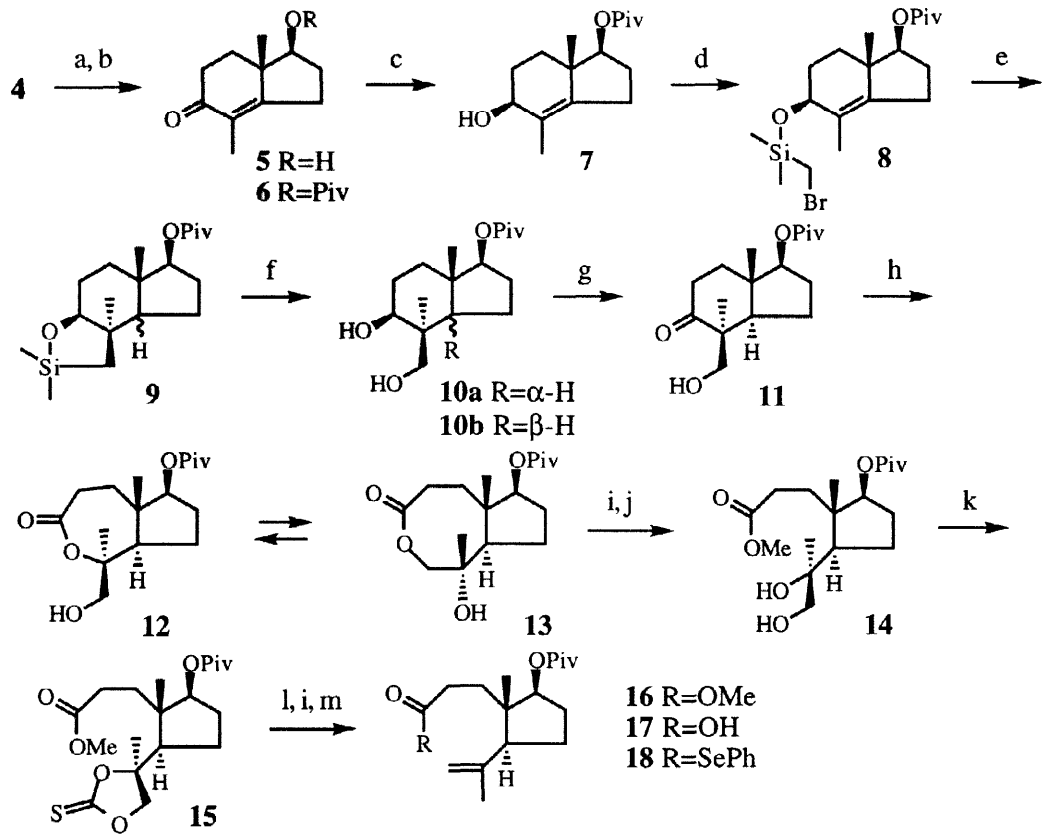
bromomethyldimethylchlorosilane to provide the silyl ether (**8**). On exposure of **8** to the radical generation conditions of Stork [6c], the reaction proceeded smoothly to give the tricyclc silyl ether (**9**), an inseparable mixture of two diastereoisomers, which was immediately treated with 30% H_2O_2 and $KHCO_3$ [9] to afford a chromatographically separable 4:1 mixtue of the requisite diol with *trans* ring juncture (**10a**) and the *cis*-isomer (**10b**) in 72% overall yield from **7**. Relative configurations at the ring juncture in (**10a,b**) were determined by n.O.e. experiments as shown in Figure 1. Selective oxidation of the secondary hydroxy group in the diol (**10a**) was cleanly achieved according to the procedure of Stevens [10]. Thus, treatment of **10a** with 7% aqueous NaOCl in acetic acid produced the perhydroindanone (**11**) in 99% yield. Interestingly, Baeyer-Villiger oxidation of **11** with *m*-CPBA led to the formation of an equilibrium mixture[1] of the 7-membered lactone (**12**) and the 8-membered lactone (**13**) in a ratio of 1:1 in 71% yield. Hydrolysis of the mixture with LiOH, followed by treatment with ethereal diazomethane, provided the diol (**14**), which was then reacted with thiocarbonyldiimidazole to give the cyclic thiocarbonate (**15**) in 67% overall yield from a mixture of the lactones.



Scheme 2. ***Reagents & Conditions***: a, $Li(^tBuO)_3AlH$, THF, 98%; b, ^tBuCOCl, 4-DMAP, pyridine, 0°C→r.t.,90%; c, $NaBH_4$, $CeCl_3$, MeOH, 0°C→r.t., 80%; d, $BrCH_2Si(Me)_2Cl$, Et_3N, 4-DMAP, CH_2Cl_2, r.t.; e, $Na(CN)BH_3$, $^nBu_3SnCl$, AIBN, ^tBuOH, reflux; f, $KHCO_3$, 30% H_2O_2, THF-MeOH(1:1), reflux, 72% for 3 steps; g, 7% aq.NaOCl, AcOH, r.t., 99%; h, *m*-CPBA, $KHCO_3$, CH_2Cl_2, r.t., 71%; i, LiOH, aq. THF, reflux; j, CH_2N_2, Et_2O, r.t., 68% for 2 steps; k, $(Imid)_2C=S$, toluene, reflux, 99%; l, $(EtO)_3P$, reflux, 70%; m, N-phenylselenophthalimide, $^nBu_3P$, THF, r.t., 70% for 2 steps.

[1] The mixture can be separated by silica gel column chromatography, but each separated product reverts immediately to the original 1:1 mixture.

Treatment of **15** with refluxing triethylphosphite [11] generated the alkenyl ester (**16**), whose methyl ester moiety was hydrolyzed, and the resulting carboxylic acid (**17**) was converted into the phenylselenyl ketone (**18**) by treatment with N-(phenylseleno)phthalimide and tri-*n*-butylphosphine [12] in 70% yield from **16**. (Scheme 2)

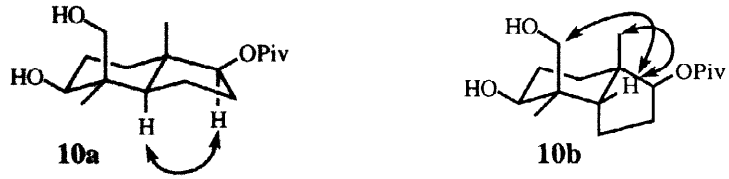
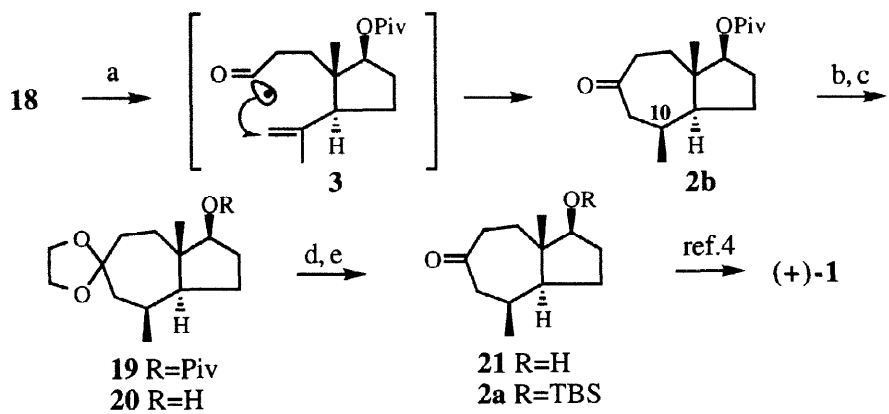


Figure 1. n.O.e. experiments for **10a** and **10b**

With the acyl radical precursor in hand, **18** was treated with tri-*n*-butyltinhydride in the presence of AIBN in refluxing toluene to give the cyclized ketone (**2b**), which would be generated via the acyl radical-mediated 7-*endo-trigonal* mode of cyclization [7], as a single product in 85% yield. Although the exact stereochemistry at the newly generated tertiary stereogenic center (C-10) in **2b** could not be determined at this stage, the confirmation was made by the following conversion. Thus, protection of the carbonyl group in **2b** by employing the protocol of Noyori [13] afforded the ketal (**19**), which was reduced with DIBAL-H to give the alcohol (**20**). Sequential acidic hydrolysis and silylation of the resulting keto alcohol (**21**) yielded **2a**, whose spectral properties, melting point, m.p. 47-49°C (lit.[4a] m.p. 48-49°C) and optical rotation, $[\alpha]_D$-32.3 (lit.[4a] $[\alpha]_D$-34.6), were identical with those reported, and the stereochemistry at C-10 in **2b** was firmly established to be the desired *S*.[2] Since the compound **2a** has already been converted into (+)-confertin (**1**) by Quinkert [4a], the present synthesis constitutes a formal total synthesis of (+)-**1**. (Scheme 3)



Scheme 3. ***Reagents & Conditions***: a, $^nBu_3SnH$, AIBN, toluene, reflux, 85%; b, $(CH_2)_2(OTMS)_2$, TMSOTf, CH_2Cl_2, -78°C, 47%; c, DIBAL-H, THF, -78°C, 88%; d, 5% HCl, THF, r.t., 99%; e, TBSOTf, 2,6-lutidine, DMF, 0°C, 99%.

In summary, we have developed a general and unprecedented methodology for the synthesis of pseudoguaianolide sesquiterpenoids by employing a highly diastereoselective acyl radical-mediated cyclization as a key reaction step and demonstrated a formal total synthesis of (+)-confertin (**1**) as an application of the procedure.

[2] The high diastereoselectivity during the radical cyclization can be explained by taking into account the transition structure of the tertiary radical intermediate, in which hydrogen abstraction should occur preferentially on the sterically less hindered α-face of the molecule.

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