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Tetrahedron Letters 45 (2004) 5569–5571
Tetrahedron Letters

The first synthesis and absolute configuration of glaucescenolide

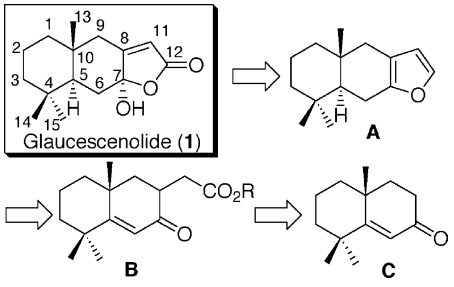
Hirosato Takikawa,* Keiko Ueda and Mitsuru Sasaki

Department of Biosystems Science, Graduate School of Science and Technology, Kobe University, Rokkodai 1-1, Nada-ku, Kobe 657-8501, Japan

Received 20 May 2004; revised 27 May 2004; accepted 31 May 2004

Abstract—The first synthesis of glaucescenolide (**1**), a cytotoxic sesquiterpene isolated from the liverwort, *Schistochila glaucescens*, was achieved by starting from 2,2,6-trimethylcyclohexanone (**2**). The absolute configuration of the naturally occurring **1** was confirmed as 5*S*,7*S*,10*R*.

In 2002, Perry et al. isolated glaucescenolide (**1**) as the main cytotoxic component in the New Zealand liverwort *Schistochila glaucescens*.[1] This sesquiterpene shows cytotoxicity against P388 mouse leukemia cells at the level of IC_{50} 2.3 μg/mL.[1] The carbon skeleton of **1** is novel in plant-derived natural products, while a few natural products with the same carbon skeleton are known from marine mollusks and sponges.[2] Although the relative configuration of three stereogenic centers in **1** was clarified, the absolute configuration remained unresolved and has been just arbitrarily proposed as shown in Scheme 1. Thus, we initiated an enantioselective synthesis of glaucescenolide **1** to determine the absolute configuration of **1** unambiguously. Herein we report the first synthesis of **1**.



Scheme 1. Structure of glaucescenolide (**1**) and its synthetic plan.

Our synthetic plan for **1** is illustrated in Scheme 1. Perry et al. have proposed a possible biosynthetic pathway, by which the hypothetical intermediate **A** is oxidized with singlet O_2 to furnish **1**.[1] Thus, the target compound **1** might be obtainable by oxidation of the intermediate **A**. For the preparation of the furan portion of **A**, an appropriate precursor should be **B**, which is readily available by installation of an acetate unit into **C**. The starting material **C** is a known compound as not only a racemate but also in optically pure form.

Our synthesis began with the preparation of the known racemic enone **3** (= **C**).[3] Among many reported procedures, we chose Duhamel's protocol[3d] because of the brevity. Although preparation of optically active **3** has been already disclosed,[4] we decided to obtain optically active **3** by developing our original methodology, because the known procedures were regarded as rather lengthy and cumbersome. Thus, we envisioned adopting enzymatic resolution. Oritani et al. have reported successful resolution of the analogous bicyclic alcohol with a lipase.[5] Diastereoselective reduction of (±)-**3** with DIBAL under Oritani's conditions[5] gave a mixture of the desired allylic alcohol (±)-**4** and its α-isomer in the ratio of 9:1. The resulting mixture was purified by SiO_2 chromatography to afford the diastereomerically enriched (±)-**4** (>96% de), which was subjected to the enzymatic resolution. Enzymatic resolution was carried out in Et_2O in the presence of vinyl acetate as an acetyl donor. After examination of ten hydrolytic enzymes, Chirazyme L-2 (Roche Diagnotics Co.) was found to be the most appropriate.[6] The optimized conditions, Chirazyme L-2 (10% to the substrate) in vinyl acetate and Et_2O at rt for 18 h, could resolve (±)-**4** almost

Keywords: Sesquiterpene; *Schistochila glaucescens*; Cytotoxicity; Enzymatic resolution.
* Corresponding author. Tel./fax: +81-78-803-5958; e-mail: takikawa@kobe-u.ac.jp

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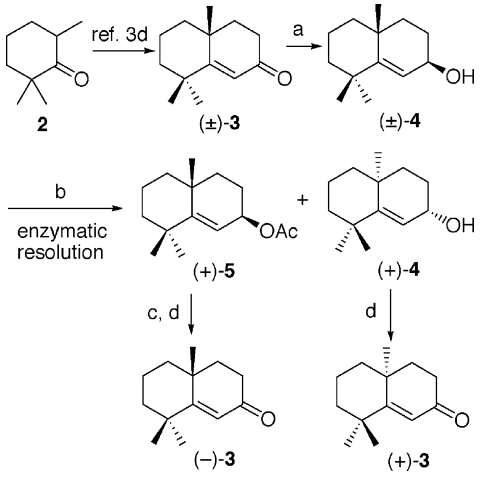
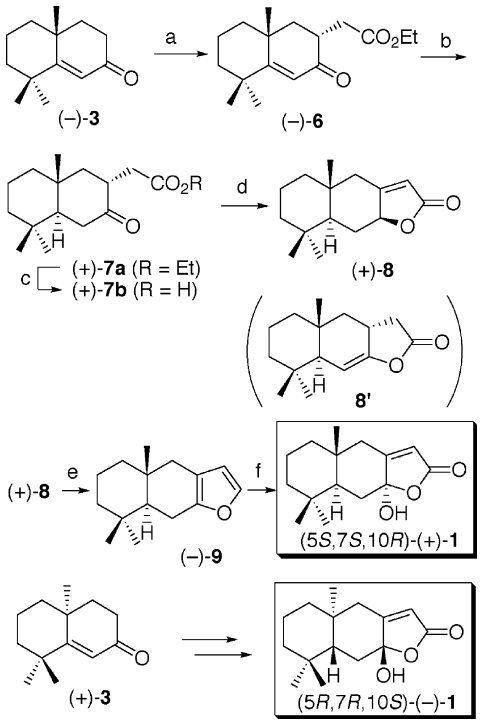
doi:10.1016/j.tetlet.2004.05.148



Scheme 2. Preparation of the optically active intermediate **3**. Reagents and conditions: (a) DIBAL, DME, THF, −78 °C (98%; α:β = 1:9); (b) Chirazyme L-2, c.-f., C2, lyo. [10 wet% to (±)-**4** as net enzyme], vinyl acetate, Et_2O, rt 18 h [47% for (+)-**4**, 48% for (+)-**5**]; (c) K_2CO_3, MeOH (97%); (d) MnO_2, $CHCl_3$ (89%).

perfectly, yielding the alcohol (+)-**4** (47%) and the enantiomeric acetate (+)-**5** (48%). The enantiomeric purity of the resulting (+)-**4** was estimated by HPLC analysis to be >99% ee.[7] The acetate (+)-**5** was converted to (−)-**4**, and its enantiomeric purity was also estimated to be 97% ee. Oxidation of (−)- and (+)-**4** with MnO_2 gave (−)- and (+)-**3**, respectively. The absolute configurations of the resulting (−)- and (+)-**3** were easily determined as shown in Scheme 2, because the reported (*R*)-**3** was levorotatory.[4a] The developed methodology for the preparation of optically active **3** or **4** is more facile than the reported procedures.[4] Therefore, this must be quite useful and versatile for the enantioselective syntheses of terpenoids, because **3** and/or its derivatives have been used for a wide range of terpenoid syntheses.[3,4,8]

With both enantiomers of **3** in hand, the remaining subjects were the construction of the furan ring and its oxidation. The enone (−)-**3** was treated with LDA and ethyl bromoacetate to give the adduct (−)-**6**. This reaction proceeded with almost perfect stereoselectivity, and no β-isomer could be detected by ^{1}H NMR analysis. The diastereofacially selective hydrogenation of enone afforded the ketoester (+)-**7a**, which was then hydrolyzed to give the ketoacid (+)-**7b**. For the formation of the γ-butenolide ring, (+)-**7b** was heated in Ac_2O in the presence of NaOAc to furnish (+)-**8** (66%) and the undesired regioisomer **8′** (<10%).[9] The resulting (+)-**8** must be kinetically and thermodynamically more preferable than its C-7 epimer, which was not detected. The next step, formation of the furan ring, was carried out by reduction with DIBAL[9a] to give (−)-**9** in good yield. The final step, oxidation of the furan ring of (−)-**9**, was successfully performed by *m*-CPBA[10] to give (+)-glaucescenolide (**1**), $[\alpha]_D^{21}$ +103 (*c* 0.102, $CHCl_3$) {lit.,[1] $[\alpha]_D^{20}$ +60 (*c* 5% $CHCl_3$)}. Similarly, (+)-**3** was also converted into (−)-**1**, $[\alpha]_D^{21}$ −101 (*c* 0.088, $CHCl_3$). The various spectral data of synthetic **1** are in good accord with those of the natural product.[11] Therefore, we were able



Scheme 3. Synthesis of glaucescenolide **1**. Reagents and conditions: (a) $BrCH_2CO_2Et$, LDA, HMPA, THF (82%); (b) H_2, Pd–C, EtOH (78%); (c) LiOH, THF, aq MeOH (90%); (d) NaOAc, Ac_2O (66%); (e) DIBAL, toluene, −78 °C (86%); (f) *m*-CPBA, $NaHCO_3$, $CHCl_3$, 0 °C (77%).

to determine the absolute configuration of the naturally occurring **1** to be 5*S*,7*S*,10*R* (Scheme 3).

In conclusion, the first synthesis of (+)- and (−)-glaucescenolide (**1**) was accomplished by starting from 2,2,6-trimethylcyclohexanone (**2**). The absolute configuration of the naturally occurring **1** was determined to be 5*S*,7*S*,10*R*. During the course of this work, we were also able to establish a concise method for the preparation of the versatile chiral building block **3** by employing enzymatic resolution. Detailed bioassays of our synthetic samples are under preparation now.

Acknowledgements

We thank Roche Diagnostics Co., Amano Enzyme Inc. and Dr. Funaki (Sumitomo Chemical Co., Ltd.) for the generous gifts of enzymes. We are grateful to Otsuka Chemical Co., Ltd. for support of this work.

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6. The other tested enzymes were as follows; Lipase AK (Amano), Lipase PS (Amano), Lipase M-AP10 (Amano), Lipase D-II (Amano), Lipase (Shin-Nihon-Kagaku-Kogyo), Lipase(BSL) (Godo Syusei), etc. Acetylation proceeded much more slowly or did not proceed with those enzymes under the same conditions.
7. HPLC analysis of (+)-**4** [column, Chiralcel® OD (4.6×250 mm); solvent, hexane:2-propanol = 100:1; flow rate, 0.5 mL/min; detection at 220 nm]: t_R/min 19.4 [>99%, (+)-**4**], 25.6 [~0%, (−)-**4**]. The enantiomeric purity of (+)-**4** was estimated to be >99% ee. $[\alpha]_D^{21}$ +50 (*c* 1.0, $CHCl_3$).
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11. Properties of synthetic (+)-**1**: colorless needles (from hexane–EtOAc); mp = 186–188 °C; $[\alpha]_D^{21}$ +103 (*c* 0.102, $CHCl_3$); IR ν_{max} (CCl_4) 3350 (m, O–H), 1740 (vs, C=O), 1655 (w, C=C) cm^{-1}; HREIMS (M^+-H_2O) obsd. 232.1455 calcd for $C_{15}H_{20}O_2$ 232.1463; ^1H NMR (300 MHz, $CDCl_3$) $\delta = 0.80$ (3H, s, 14-H_3), 0.84 (3H, s, 13-H_3), 0.95 (3H, s, 15-H_3), 1.25 (1H, ddd, $J = 13$, 13, 4 Hz, 3-H_{ax}), 1.33 (1H, ddd, $J = 13$, 13, 3 Hz, 1-H_{ax}), 1.42–1.71 (6H, m, 1-H_{eq}, 2-H_2, 3-H_{eq}, 5-H, 6-H_{ax}), 2.28 (2H, br s, 9-H_2), 2.35 (1H, d, $J = 13$ Hz, 6-H_{eq}), 2.95 (1H, br s, OH), 5.72 (1H, br s, 11-H); ^{13}C NMR (75 MHz, $CDCl_3$) $\delta = 18.7$, 19.0, 21.4, 32.9, 33.2, 35.4, 38.5, 41.7, 41.8, 44.8, 48.8, 105.1, 114.9, 167.8, 170.5. (−)-**1**: $[\alpha]_D^{21}$ −101 (*c* 0.088, $CHCl_3$); HREIMS (M^+-H_2O) obsd. 232.1455 calcd for $C_{15}H_{20}O_2$ 232.1463. Other spectral data were identical with those of (+)-**1**.