Stereocontrolled Synthesis of a Tetracyclic Sesterterpene, (+)-Scalarenedial

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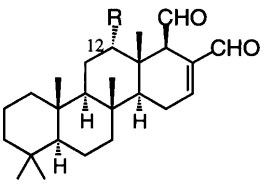
(Received August 14, 2000; CL-000774)

A stereocontrolled, formal synthesis of a tetracyclic sesterterpene, (+)-scalarenedial, was achieved by means of repeating the same ring construction method and a simple resolution of the intermediary tetracyclic β-ketoester with a chiral auxiliary.

In our program to develop a simple method for providing enantiomerically pure bi-, tri-, and tetracyclic frameworks having a 1,1,5-trimethyl-*trans*-decalin nucleus and to demonstrate its utility for terpenoid synthesis, we have already reported the stereocontrolled total syntheses of (+)-acuminolide as a bicyclic diterpene[1] and (–)-spongianolide A as a tricyclic sesterterpene.[2] As the next step, we tried to apply the method thus developed to the synthesis of tetracyclic terpenoids. As the target molecule, we selected scalarenedial (**1**),[3] which is 12-deacetoxyscalaradial,[4] and contains a characteristic 6/6/6/6 fused ring system. This pentaprenoid displays not only fish anti-feedent property but also antitumor and anti-inflammatory effects, and also strongly inhibits the hydrolytic ability of phospholipase A_2

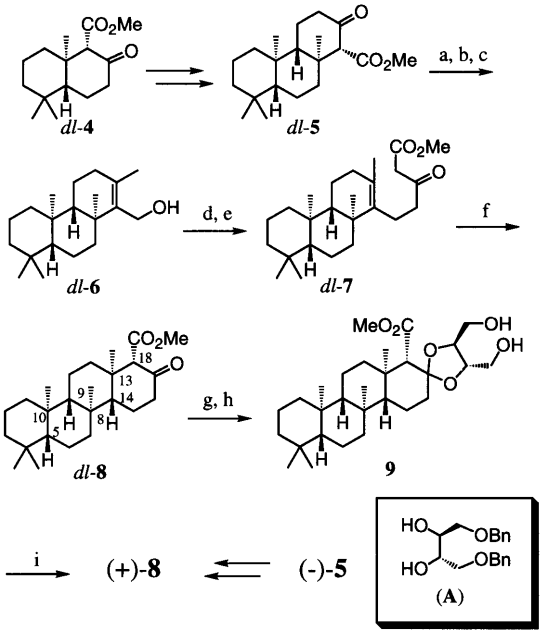


(-)-Scalarenedial (**1**) : R = H
(+)-Scalaradial (**2**) : R = OAc

(PLA_2). In connection with our interest in elucidating the inhibitory mechanism of PLA_2 by some unsaturated aldehyde terpenoids,[5] the stereocontrolled simple synthesis of the enantiomerically pure tetracyclic scalarenedial was also a very attractive subject in addition to the further demonstration of our own simple method for providing an enantiomerically pure cyclic frameworks for terpenoid synthesis. The first enantioselective total synthesis of (–)-scalarenedial (**1**) was reported by Corey and co-workers via a biomimetic route involving the enantiospecific tetracyclization reaction.[6] In this paper, we describe the simple, stereocontrolled synthesis of enantiomerically pure tetracyclic diol **3**, which had been transformed into scalarenedial by Corey's group, by means of repeating the same sequence of reactions for the ring construction using olefin cyclization and a simple resolution method.

As shown in Scheme 1, tetracyclic β-ketoester **8** was obtained from **5**[2] by enol phosphonate formation, introduction of a methyl group with lithium dimethylcuprate, and reduction of the ester group with $LiAlH_4$ to give **6** (89% yield for three steps), which was transformed into linear β-ketoester **7** by bromination and condensation with methyl acetoacetate in 83% yield. The successful cyclization of **7** into tetracyclic β-

Scheme 1.

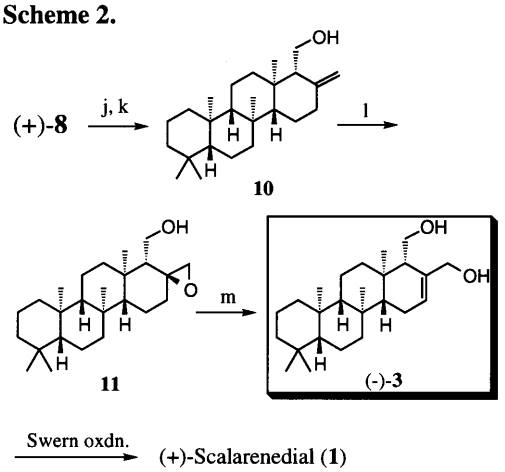


a) NaH, $ClP(O)(OEt)_2$, THF, rt, 1 h; b) MeLi, CuI, ether, -40 to 0 °C, 30 min; c) $LiAlH_4$, ether, rt, overnight, 89% for 3 steps; d) PBr_3, pyridine, ether, 0 °C, 30 min.; e) methyl acetoacetate, NaH, *n*-BuLi, THF, 0 °C, overnight, 83% for 2 steps; f) $SnCl_4$, CH_2Cl_2, rt, 20-40 h, 64%; g) (**A**), *p*-TsOH, C_6H_6, 90 °C, 2 h; h) Pd-C, H_2, AcOEt, rt, overnight, 89% for 2 steps; i) 2N H_2SO_4 aq., MeOH, THF, 90 °C, 2 d, 85%.

ketoester **8** was fortunately achieved by treatment with tin tetrachloride in 64% yield. The relatively lower solubility of **7** in CH_2Cl_2 and the characteristic 6/6/6/6 fused ring system did not seriously impede the ring construction. The resolution of the enantiomers of **8** was achieved by utilization of a chiral auxiliary, 1,4-*O*-dibenzyl-L-threitol (**A**),[7] for acetal formation, which was followed by removal of the benzyl groups to give diol **9**. The diastereomers of **9** were nicely separated by column chromatography on silica gel (eluted with $CHCl_3$ contained from 1% to 3% MeOH). Hydrolysis of the acetal under acid conditions gave the enantiomerically pure (+)-**8**[8] and (–)-**8**. One of the enantiomers, (+)-**8**, was also synthesized from the enantiomerically pure tricyclic compound, (–)-**5**, whose absolute configuration had already been determined.[2] Therefore, the absolute configuration of (+)-**8** was determined as (5*R*,8*S*,9*S*,10*R*,13*R*,14*R*,18*S*). Synthesis of an antipode of scalarenedial from (+)-**8** is shown in Scheme 2. The successful Wittig olefination of (+)-**8** with excess triphenylphosphonium methylide in THF at room temperature for 10 min followed by reduction of the ester group produced alcohol **10** in 70% yield for two steps. Use of one equivalent of the Wittig reagent

required longer reaction time, and caused severe isomerization of the ester group. Epoxidation of the *exo*-methylene moiety with mCPBA stereoselectively produced the corresponding epoxide **11** as a single isomer in 85% yield. Regioselective introduction of the C16–C17 double bond was successful by treatment of **11** with camphorsulfonic acid in THF–water at 80 °C for 3 h to produce the desired (–)-**3** in 53% yield.[9] The spectral and physical data except the sign of the optical rotation of this synthesized diol **3** were in good agreement with those reported.[6,10] Transformation from diol **3** to scalarenedial (**1**) had already been achieved by Corey's group. Thus, the formal synthesis of scalarenedial was achieved, and the present synthesis further demonstrated that the method applied for the ring construction and the simple resolution were viable and general for the synthesis of the enantiomerically pure terpenoids having a 1,1,5-trimethyl-*trans*-decalin nucleus.

Scheme 2.



j) $MeP^+Ph_3Br^-$, $NaNH_2$, THF, rt, 10 min; k) $LiAlH_4$, THF, rt, 12 h, 70% for 2 steps; l) mCPBA, $NaHCO_3$, CH_2Cl_2, rt, 1 h, 85%; m) CSA, THF, H_2O, 80 °C, 3 h, 53%.

This work was partially supported by a Grant-in-Aid for Scientific Research 09480415 from the Ministry of Education, Science, Sports, and Culture of Japan.

References and Notes

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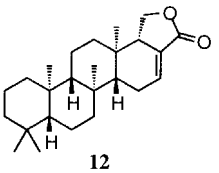
8 Data for (+)-**8**; mp 220–221 °C; $[\alpha]_D^{21}$ +20.19° (*c* 0.312, $CHCl_3$); IR (KBr, cm^{-1}) 1746, 1719; ^1H NMR (400 MHz, $CDCl_3$) δ 3.68 (s, 3H), 3.21 (s, 1H), 2.47 (ddd, 1H, *J* = 14.6, 5.2, 1.7 Hz), 2.29 (m, 1H), 1.98 (m, 1H), 0.70–1.85 (m, 18H), 1.16 (s, 3H), 0.90 (s, 3H), 0.86 (s, 3H), 0.83 (s, 3H), 0.81 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 205.57, 168.59, 70.02, 61.20, 58.32, 56.55, 51.41, 42.40, 42.05, 41.99, 40.87, 40.49, 39.90, 38.28, 37.50, 33.27, 21.85, 21.30, 18.59, 18.19, 17.26, 17.22, 16.31, 15.35; Anal. Found: C, 77.19; H, 10.43%. Calcd for $C_{25}H_{40}O_3$: C, 77.27; H, 10.37%.

9 Data for (–)-**3**; mp 214–216 °C; $[\alpha]_D^{21}$ –6.80° (*c* 0.196, $CHCl_3$); IR (KBr, cm^{-1}) 3360, 2920, 2845, 1721, 1672; ^1H NMR (400 MHz, $CDCl_3$) δ 5.78 (m, 1H), 4.35 (d, 1H, *J* = 12.0 Hz), 3.98 (d, 1H, *J* = 12.0 Hz), 3.90 (dd, 1H, *J* = 10.8, 2.0 Hz), 3.69 (dd, 1H, *J* = 10.8, 8.5 Hz), 0.75–2.20 (m, 20H), 0.89 (s, 3H), 0.87 (s, 3H), 0.84 (s, 3H), 0.83 (s, 3H), 0.72 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 136.64, 127.55, 67.45, 61.51, 60.79, 56.42, 54.95, 54.70, 42.13, 41.73, 41.06, 39.86, 37.58, 37.39, 35.57, 33.29, 22.50, 21.37, 18.61, 18.15, 17.63, 16.78, 16.42, 15.31.

10 The obtained diol **3** was transformed into lactone **12** by MnO_2 oxidation. The spectral and physical data of **12**, except the sign of the optical rotation, were in good agreement with those reported.[6]



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