Stereocontrolled Synthesis of (+)-Acuminolide and Determination of Its Absolute Configuration

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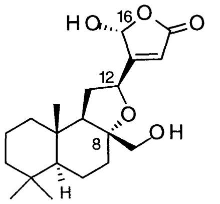
As a demonstration for an easy supply of the enantiomerically pure intermediate for the synthesis of labdane diterpenoids, stereocontrolled synthesis of (+)-acuminolide was achieved, and its absolute configuration was determined.

(+)-Acuminolide was isolated from the stem bark of *Neouvaria acuminatissima* (a tree found in tropical rain forests), and was reported to display cytotoxic activity in human cancer cell lines and cultured P388 cells.[1] The structure of this highly oxidized diterpene was determined on the basis of spectroscopic and chemical methods as well as X-ray crystallography and was depicted as the formula **1**, while its absolute configuration has not been confirmed yet. The first synthesis of this labdane diterpene having γ-hydroxybutenolide and tetrahydrofuran ring moieties was reported in 1998.[2] In that synthesis, since commercially available (+)-sclareolide was used as the starting material, the regioselectivity for the preparation of the desired intermediate was not controlled; also the stereoselectivity for the construction of the C-12 asymmetric center was poor. In addition, the optical rotation value of the synthesized acuminolide was not mentioned at all, although ^{1}H and ^{13}C-NMR data and mp showed good agreement with those of the natural product.

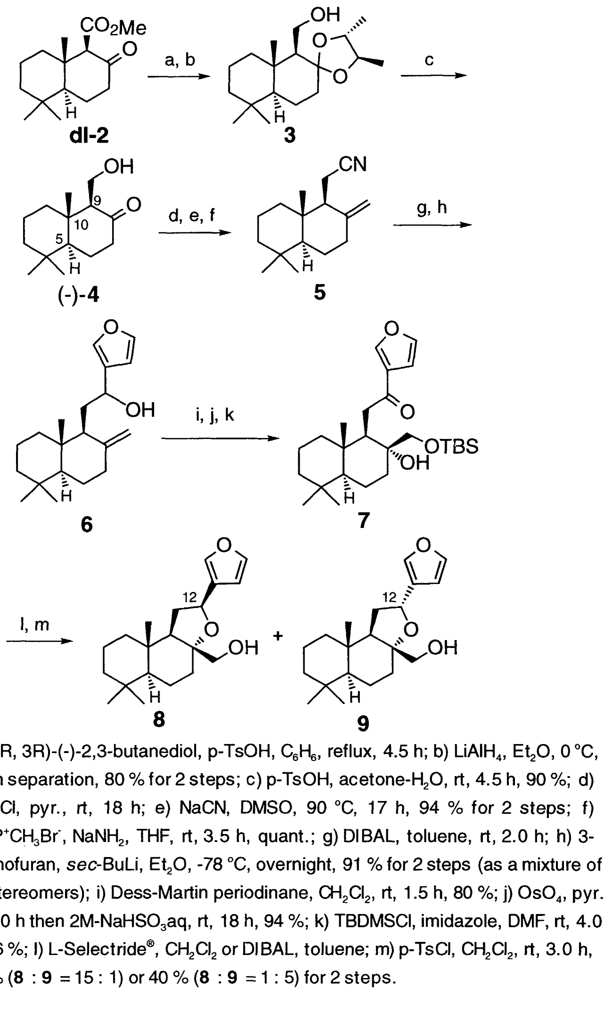


Acuminolide (**1**)

In our program to develop a simple method for providing enantiomerically pure bicyclic, tricyclic, and tetracyclic frameworks having a 1,1,5-trimethyl-*trans*-decalin nucleus and to demonstrate their utility for terpenoid synthesis,[3] we selected (+)-acuminolide as a target molecule in the terpenoid having a bicyclic framework. We now report the stereocontrolled synthesis of (+)-acuminolide by means of a simple resolution method of the intermediary β-ketoester, followed by highly diastereoselective reduction of the ketone and then cyclization. The present synthesis has revealed that the absolute configuration of (+)-acuminolide is ent-form against the usual labdane diterpene as shown in Scheme 2.

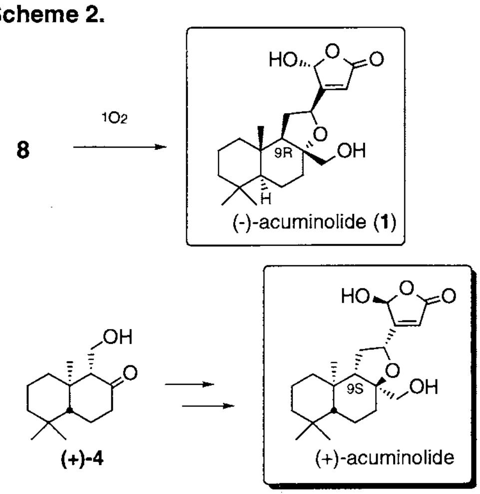
As a versatile chiral intermediate for the synthesis of the labdane terpenoids, we chose racemic β-ketoester **2**.[4] Acetal formation of **2** with (2*R*,3*R*)-(-)-2,3-butanediol followed by reduction of the ester group gave alcohol **3**. The diastereomers of **3** were nicely separated by column chromatography on silica gel (eluted with hexane containing from 2% to 10% AcOEt).[5] After hydrolysis of the acetal, the enantiomerically pure (-)-**4** was obtained, and its physico-chemical data were in good agreement with those of reported (-)-**4**, whose absolute configuration had been determined as (5*S*,9*S*,10*S*) in labdane type numbering by the transformation into a sesquiterpene, (1*S*,4a*S*,8a*S*)-(+)-albicanol.[6] The compound **4** was transformed into nitrile **5** by a sequence of tosylation, cyanation, and then the Wittig reaction with triphenylphosphonium methylide in 94% yield for three steps. DIBAL reduction of the nitrile yielded the corresponding aldehyde, which was reacted with 3-lithiofuran prepared from 3-bromofuran and *sec*-BuLi *in situ* at -78 °C to produce secondary alcohol **6** in 91% yield for two steps as a mixture of diastereoisomers. The successful oxidation of **6** with Dess-Martin periodinane yielded the corresponding ketone,[7] whose exomethylene group was oxidized with OsO_4 to produce the corresponding diol as a single stereo-

Scheme 1.



a) (2R, 3R)-(-)-2,3-butanediol, p-TsOH, C_6H_6, reflux, 4.5 h; b) $LiAlH_4$, Et_2O, 0 °C, 3.0 h separation, 80 % for 2 steps; c) p-TsOH, acetone-H_2O, rt, 4.5 h, 90 %; d) p-TsCl, pyr., rt, 18 h; e) NaCN, DMSO, 90 °C, 17 h, 94 % for 2 steps; f) $Ph_3P^+CH_3Br^-$, $NaNH_2$, THF, rt, 3.5 h, quant.; g) DIBAL, toluene, rt, 2.0 h; h) 3-bromofuran, *sec*-BuLi, Et_2O, -78 °C, overnight, 91 % for 2 steps (as a mixture of diastereomers); i) Dess-Martin periodinane, CH_2Cl_2, rt, 1.5 h, 80 %; j) OsO_4, pyr. rt, 3.0 h then 2M-$NaHSO_3$aq, rt, 18 h, 94 %; k) TBDMSCl, imidazole, DMF, rt, 4.0 h, 96 %; l) L-Selectride®, CH_2Cl_2 or DIBAL, toluene; m) p-TsCl, CH_2Cl_2, rt, 3.0 h, 80 % (**8** : **9** = 15 : 1) or 40 % (**8** : **9** = 1 : 5) for 2 steps.

Scheme 2.



isomer. Protection of the primary hydroxy group of the diol with a *tert*-butyldimethylsilyl group afforded ketone **7**.[8] The diastereoselective reduction of the carbonyl group of **7** was then examined. L-Selectride® reduction of **7** followed by acid treatment produced cyclic ether **8** along with its stereoisomer **9** in a ratio of 15 : 1 by ^{1}H NMR in 80% yield resulting from the stereoselective reduction, cyclization and deprotection.[9,10] On the other hand, reduction of **7** with DIBAL followed by acid treatment gave **9** as a major product in 40% yield (**8** : **9** = 1 : 5 by ^{1}H NMR).[11] The spectral data of both **8** and **9** obtained here were in good agreement with those of the reported compounds, respectively, whose stereochemistry had already been determined.[2] The synthesis of acuminolide (**1**) was achieved by photosensitized oxygenation of **8** in the presence of a catalytic amount of tetraphenylporphine and excess amount of ethyldiisopropylamine in CH_2Cl_2 at -78 °C in a similar manner as reported.[2] The spectral data and mp of the synthesized acuminolide, which was obtained as the major stereoisomer at C-16, were in good agreement with those of the natural product (mp 207.0-208.0 °C, literature, mp 207-208 °C). However, to our surprise, the sign of the optical rotation showed a minus, which is contrary to that of the natural product. Then, we synthesized (+)-acuminolide starting from (+)-**4** by the same procedure. The melting point of a mixture of synthesized (+)-compound (mp 207.5-208.5 °C, $[a]_D^{22}$ 34.6 (c 0.85, $CHCl_3$)) and natural (+)-acuminolide showed no decrease. Thus, the absolute configuration of the natural (+)-acuminolide was determined as (5*R*, 8*S*, 9*S*, 10*R*, 12*R*) by the present synthesis.

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Reference and Notes

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5 Data for (-)-**3** ; mp 122.5-123.0 °C; $[\alpha]_D^{25}$ -15.9 (c 1.00, $CHCl_3$); ^{1}H NMR(400 MHz, $CDCl_3$) δ 3.91(dd, 1H, *J* = 7.2, 10.8 Hz), 3.80(m, 1H), 3.63(m, 1H), 3.55(m, 1H), 3.00(d, 1H, *J* = 8.4 Hz), 1.93(m, 1H), 1.82(m, 1H), 1.30(d, 3H, *J* = 6.1 Hz), 1.23(d, 3H, *J* = 6.1 Hz), 1.08 - 1.62(m, 9H), 0.87(s, 3H), 0.86(s, 3H), 0.81(s, 3H); Anal. Found: C, 72.72; H, 10.90%. Calcd. for $C_{18}H_{31}O_3$: C, 72.91; H, 10.89%.

6 K. Shishido, Y. Tokunaga, N. Omachi, K. Hiroya, and K. Fukumoto, *J. Chem. Soc., Perkin Trans. 1*, **1999**, 2481.

7 Oxidation with $BaMnO_2$, MnO_2, PCC, PDC, and actived DMSO gave poor yield of the corresponding ketone.

8 Data for (-)-**7** ; mp 124.5-126.0 °C; $[\alpha]_D^{23}$ -4.5 (c 0.63, $CHCl_3$); ^{1}H NMR(400 MHz, $CDCl_3$) δ 8.23(s, 1H), 7.41(brs, 1H), 6.81(brs, 1H), 3.65(d, 1H, *J* = 9.8 Hz), 3.41(dd, 1H, *J* = 1.5, 9.8 Hz), 3.17(s, 1H), 3.08(dd, 1H, *J* = 3.0, 16.1 Hz), 2.40(dd, 1H, *J* = 3.0, 7.6 Hz), 2.11(dt, 1H, *J* = 3.0, 12.7 Hz), 1.10 - 1.70(m, 10H), 0.91(s, 9H), 0.86(s, 3H), 0.79(s, 6H), 0.09(s, 6H); ^{13}C NMR(100MHz, $CDCl_3$) δ 195.9, 147.5, 143.7, 127.4, 109.1, 73.2, 64.2, 55.7, 54.1, 41.6, 39.3, 38.5, 37.8, 36.9, 33.3, 33.1, 25.9, 21.5, 20.0, 18.33, 18.25, 15.7, -5.4; IR (KBr, cm^{-1}) 3530, 3125, 1672; EI^+ HRMS Found m/z 448.2984, Calcd. for $C_{26}H_{44}O_4Si$ M^+ 448.3009.

9 The diastereoisomers of the alcohol resulting from the reduction of **7** were not distinguishable from one another by TLC and ^{1}H NMR.

10 Treatment of the crude alcohol which was obtained from **7** by L-Selectride® reduction, with *p*-TsCl in pyridine gave the same result as that of the acid treatment. These results clearly show that the reduction stereoselectively proceeded to exclusively produce the (12*R*)-stereoisomer.

11 Although we obtained the most stable conformation of the compound **7** by means of molecular mechanics calculation, we could not draw the clear conclusion to understand the stereoselectivity of the reductions.