The First Total Synthesis of Natural (+)-Terpestacin, Syncytium Formation Inhibitor

Sir:

During the search for drugs to cure AIDS, Bristol-Myers Squibb's group has isolated terpestacin (**1**) from culture broth of *Arthrinium* sp. as a novel syncytium formation inhibitor, which is expected to be an anti-HIV drug[1], and determined the absolute structure mainly by NMR studies and X-ray single-crystal analysis to be a bicyclo 5, 15-fused sesterterpene **1**[2]. Independently, the almost same compound has been reported as a phytotoxin from *Bipolaris cynodontis*[3].

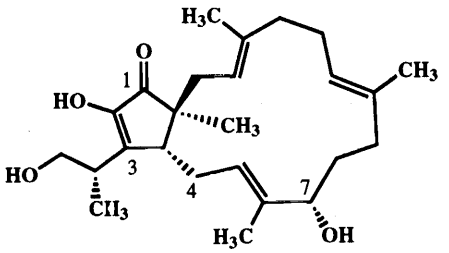
Very recently, we have synthesized racemic terpestacin [(±)-**1**] from racemic 2-cyclopenten-1-yl acetic acid [(±)-**2**] and *E,E*-farnesol through *C*-alkylation of the tricyclic compound (±)-**6** as shown in Scheme 1[4].

Iodo-lactonization of (±)-**2** followed by S_N2-type hydrolysis and *O*-silylation gave the bicyclic β-alcohol (±)-**3**, which was converted into the keto-ester (±)-**4** in seven steps. Michael addition of a vinyl group to (±)-**4** furnished the enol ester (±)-**5**, which was led to the key lactone (±)-**6** in three steps.

The chain portion **8** was prepared as a single isomer from *E,E*-farnesol through the aldehyde **7** in six steps[4]. The stereochemistry was not determined, since both asymmetries at *C*1 and *C*2 would be lost later on (namely: from **9** to **19**).

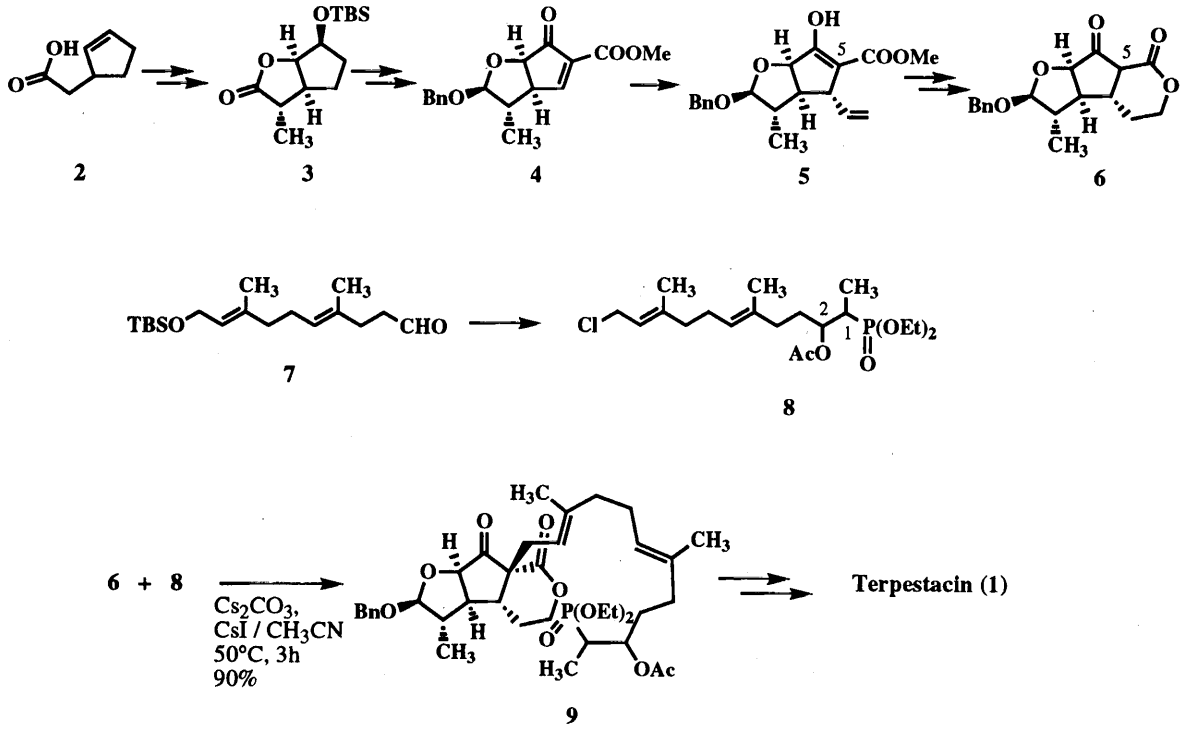
The alkylation of (±)-**6** with **8** was achieved in the presence of Cs_2CO_3 and CsI to give exclusively and stereoselectively the desired *C*-alkylated product (±)-**9**, which, in turn, was converted into terpestacin [(±)-**1**] through the construction of proper configurations and functionalities.

Herein, we describe the first and enantiospecific total synthesis of natural terpestacin (**1**) to confirm the absolute structure. Our synthesis was designed around the use of tri-*O*-acetyl-D-galactal **10** as a chiral source to set the key intermediate **6** and natural configurations.

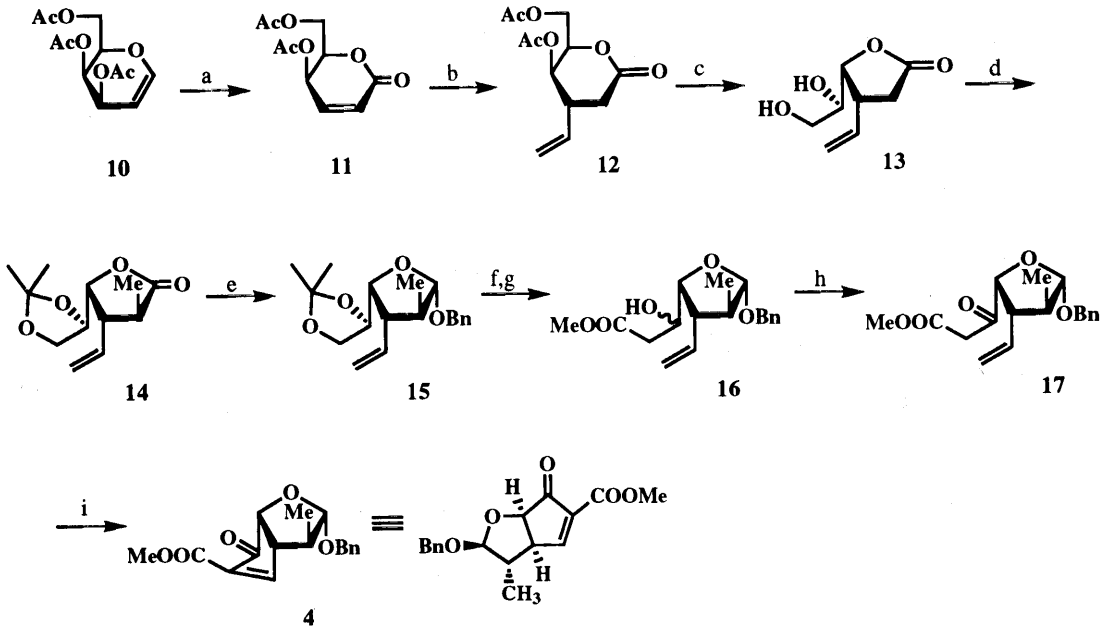


Terpestacin (**1**)

Scheme 1.



Scheme 2.



Conditions; (a) mCPBA, $BF_3 \cdot Et_2O/CH_2Cl_2$, 0°C, 0.5 hour (b) $H_2C=CHMgBr$, Bu_3P, CuI/Et_2O, −78°C, 0.25 hour; 70% (c) 2% HCl-MeOH, rt, 10 hours; 80% (d) 1) $(CH_3O)_2C(CH_3)_2$, PPTS/CH_2Cl_2, rt, 2 hours 2) LiHMDS, MeI/THF, −78°C, 0.5 hour; 77% (e) 1) DIBAL-H/Toluene, −78°C, 0.5 hour 2) NaH, BnBr, TBAI/THF, 50°C, 0.5 hour; 66% (f) 1) 80% AcOHaq, rt, 2 hours 2) $NaIO_4$/THF-H_2O, rt, 2 hours; 88% (g) LiHMDS, AcOMe/THF, −78°C, 0.5 hour; 78% (h) DMSO, DCC, Py-TFA/Et_2O, rt, 3 hours; 88% (i) 1) O_3, then PPh_3/CH_2Cl_2, −78°C, 2 hours 2) NaOMe/MeOH, rt, 2 hours; 70%.

The galactal **10** was oxidized to the lactone **11**[5], where the vinyl group was introduced from the sterically less-encumbered face to give **12** [EI-MS *m/z* 257 $(M+H)^+$] in 70% yield in 2 steps (Scheme 2 and Table 1). The δ-lactone **12** was de-*O*-acetylated to produce the γ-lactone **13** through ester migration. This lactone **13**, after protection of the diol, reacted with MeI also on the less-hindered site to give stereoselectively **14**. Hydride reduction of **14** followed by *O*-benzylation gave predominantly the furanoside **15**. Removal of the *O*-isopropylidene group, periodate cleavage of the diol, and reaction of the resulting aldehyde with lithiated methyl acetate provided the hydroxy ester **16** [EI-MS *m/z* 321 $(M+H)^+$]. This was oxidized to the keto ester **17** [EI-MS *m/z* 318 (M^+)] which, after ozonolysis, underwent effective aldol condensation to give the bicyclic compound **4** [EI-MS *m/z* 304 (M^+)]. Conjugate addition of a vinyl group to the convex face of **4** to give **5** (Scheme 1), followed by hydroboration and lactonization, afforded the key compound **6** [EI-MS *m/z* 316 (M^+)] as a diastereomeric mixture at C5. This mixture was then submitted to the *C*-alkylation with the allyl chloride **8** to give **9** [FAB-MS *m/z* 703 $(M+H)^+$] as mentioned above. Compound **9** was converted into natural terpestacin (**1**) by our previously reported procedures[4] except for stereoselective reduction of the ketone **21** to the α-alcohol **22** as follows (Scheme 3).

Horner-Emmons cyclization of **18**, which was derived from **9** in 5 steps, afforded a single product **19** [FAB-MS *m/z* 581 $(M+H)^+$]. Selective hydride reduction at C7† of **19**, followed by *O*-silyl protection and $LiAlH_4$ reduction, gave the primary alcohol **20**, the relative stereochemistry of which was confirmed by NOE studies[4]. Compound **20** was converted into the ketone **21** through Wolff-Kishner reduction of the intermediary aldehyde and MnO_2 oxidation of the allyl alcohol. The stereoselective reduction in question of the C7 carbonyl group of **21** was assayed under a variety of conditions. The best result was realized by modified Noyori's conditions[6] using (*S*)-BINAL-H in CH_2Cl_2-THF (4:1) to give a 5:1 mixture of α-alcohol (**22**) and β-alcohol, while the racemic ketone [(±)-**21**] was reduced to a 2:1 mixture of the alcohols. After reductive opening of the furanose ring and selective *O*-benzoylation of the primary

† The carbon-numbering protocol parallels conveniently the nomenclature of the natural product **1**.

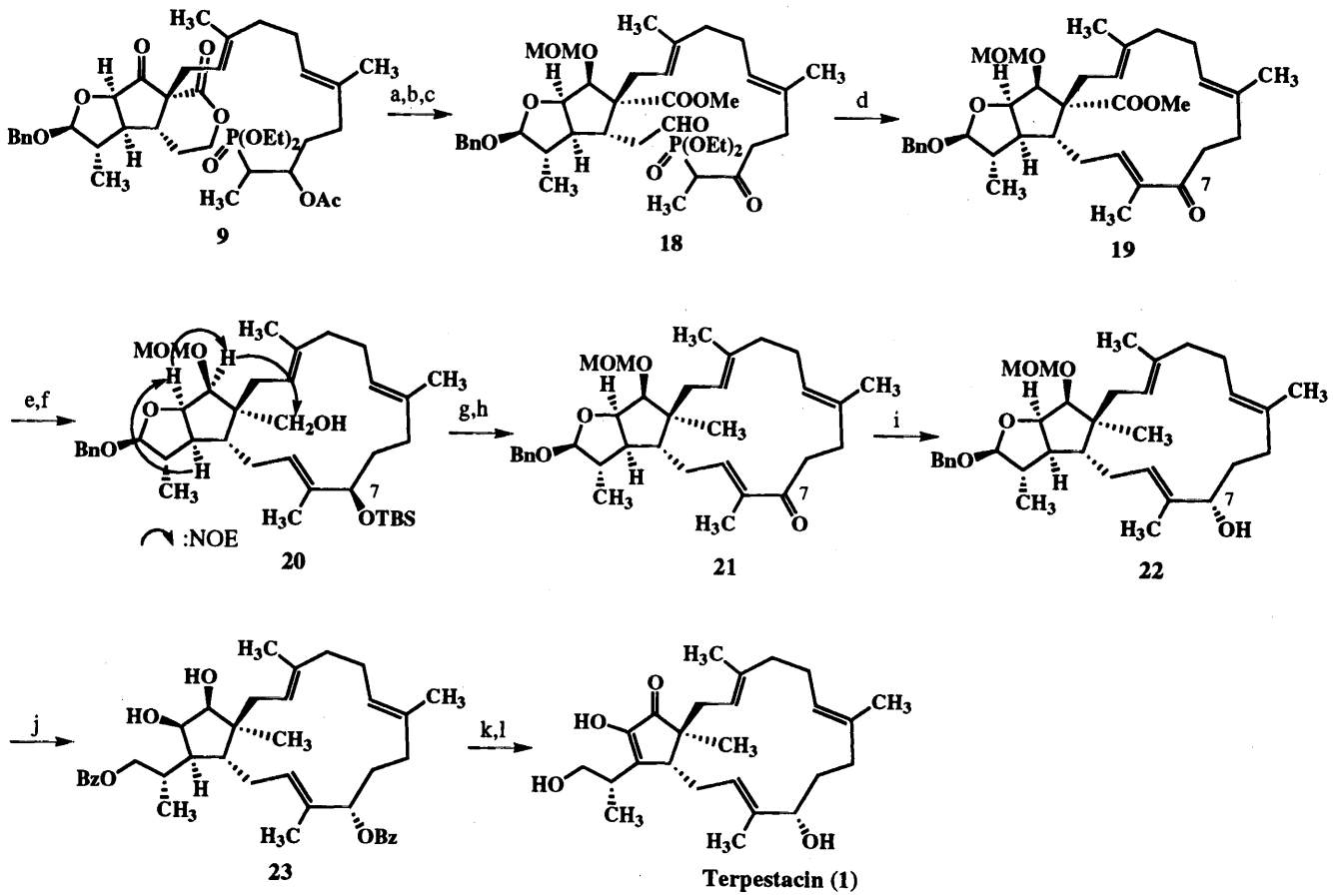
Table 1-1. Physico-chemical properties of compounds.

No.	MP (°C)	$[\alpha]_D$ ($CHCl_3$)	^{1}H-NMR (270 or 400 MHz; $CDCl_3$; δ ppm; J Hz)
1	171~172	+27° (*c* 0.22)	δ 0.98 (3H, s), 1.28 (3H, d, J=7.2), 1.62 (3H, s), 1.63 (3H, s), 2.37 (1H, dd, J=10.4, 13.8), 2.43 (1H, br d, J=16.8), 2.69 (1H, dd, J=2.4, 11.0), 3.80 (1H, dd, J=5.4, 11.0), 3.87 (1H, dd, J=5.2, 11.0), 4.04 (1H, dd, J=3.0, 10.0), 5.12 (1H, m), 5.23 (1H, m), 5.39 (1H, m).
4	137~138	+68° (*c* 0.86)	δ 1.14 (3H, d, J=7.2), 2.38 (1H, dq, J=1.2, 7.2), 3.08 (1H, ddd, J=1.2, 3.2, 6.0), 3.80 (3H, s), 4.24 (1H, d, J=13.4), 4.56 (1H, d, J=13.4), 4.65 (1H, d, J=6.0), 4.91 (1H, s), 7.25 (5H, m), 8.33 (1H, d, J=3.2).
9	Syrup		δ 1.07 (3H, d, J=7.0), 1.23 (3H, dd, J=7.4, 9.0), 1.38 (3H, s), 1.56 (3H, s), 2.05 (3H, s), 4.45 (2H, dd, J=3.2, 10.0), 4.79 (1H, d, J=9.8), 4.96 (1H, t, J=7.6), 5.03 (1H, t, J=6.4), 5.19 (1H, ddd, J=4.0, 10.0, 18.0).
11	Syrup	−349° (*c* 1.12)	δ 2.10 (3H, s), 2.11 (3H, s), 4.36 (1H, d, J=6.2), 4.37 (1H, d, J=5.8), 4.77 (1H, ddd, J=2.4, 5.8, 6.2), 5.30 (1H, dd, J=2.4, 5.6), 6.25 (1H, d, J=9.2), 7.01 (1H, dd, J=5.6, 9.2).
12	Syrup	+52° (*c* 1.17)	δ 2.07 (3H, s), 2.14 (3H, s), 2.63 (1H, dd, J=4.4, 17.8), 2.82 (1H, dd, J=6.4, 17.8), 2.92 (1H, m), 4.21 (1H, dd, J=7.0, 11.4), 4.27 (1H, dd, J=5.6, 11.4), 4.67 (1H, ddd, J=3.2, 5.6, 7.0), 5.11 (1H, dd, J=3.0, 3.2), 5.25 (1H, dd, J=1.6, 17.6), 5.33 (1H, dd, J=1.6, 10.4), 5.89 (1H, ddd, J=5.6, 10.4, 17.6).
13	Syrup	−50° (*c* 1.17)	δ 2.58 (1H, dd, J=9.0, 17.6), 2.75 (1H, dd, J=10.2, 17.6), 3.24 (1H, m), 3.75 (2H, br s), 3.88 (1H, br s), 4.50 (1H, dd, J=2.0, 8.4), 5.24 (1H, br d, J=17.8), 5.26 (1H, br d, J=8.6), 5.99 (1H, ddd, J=8.6, 9.6, 17.8).
14	112~113	−73° (*c* 1.04)	δ 1.18 (3H, d, J=6.8), 1.37 (6H, s), 2.77 (1H, dq, J=6.8, 13.6), 2.88 (1H, dt, J=8.2, 13.6), 3.98 (1H, t, J=8.2), 4.06 (1H, dd, J=6.6, 8.2), 4.23 (1H, ddd, J=1.0, 6.6, 8.2), 4.35 (1H, dd, J=1.0, 8.2), 5.26 (1H, dd, J=1.6, 11.0), 5.27 (1H, dd, J=1.6, 17.8), 5.92 (1H, ddd, J=8.2, 11.0, 17.8).
15	Syrup	+35° (*c* 1.27)	δ 1.05 (3H, d, J=6.8), 1.36 (3H, s), 1.45 (3H, s), 2.26 (1H, m), 2.50 (1H, dt, J=5.0, 9.6), 3.61 (1H, dd, J=6.8, 7.6), 4.00 (1H, dd, J=6.0, 7.6), 4.16 (2H, m), 4.51 (1H, d, J=12.2), 4.87 (1H, d, J=2.4), 4.89 (1H, d, J=12.2), 5.03 (1H, dd, J=1.8, 17.6), 5.05 (1H, dd, J=1.8, 9.6), 6.00 (1H, ddd, J=9.6, 10.8, 17.6), 7.35 (5H, m).
16	Syrup	+8.6° (*c* 1.33)	δ 1.06 (3H, d, J=7.6), 2.21 (1H, ddq, J=2.8, 7.2, 7.6), 2.54 (1H, dd, J=8.4, 15.0), 2.62 (1H, dt, J=7.2, 9.6), 2.75 (1H, dd, J=3.0, 15.0), 2.94 (1H, d, J=3.0), 3.70 (3H, s), 4.03 (1H, t, J=7.2), 4.22 (1H, ddd, J=3.0, 7.2, 8.4), 4.49 (1H, d, J=11.8), 4.75 (1H, d, J=11.8), 4.81 (1H, d, J=2.8), 5.14 (1H, dd, J=1.2, 17.0), 5.16 (1H, dd, J=1.2, 9.6), 6.14 (1H, dt, J=9.6, 17.0), 7.33 (5H, m).
17	Syrup	+93° (*c* 1.99)	δ 1.06 (3H, d, J=7.0), 2.20 (1H, m), 2.77 (1H, m), 3.52 (1H, d, J=16.2), 3.72 (1H, d, J=16.2), 3.74 (3H, s), 4.58 (1H, d, J=11.6), 4.69 (1H, d, J=8.4), 4.93 (1H, d, J=11.6), 4.97 (1H, d, J=3.6), 5.08 (1H, dd, J=1.6, 15.6), 5.09 (1H, dd, J=1.6, 11.0), 5.83 (1H, ddd, J=9.0, 11.0, 15.6), 7.36 (5H, m).
18	Syrup		δ 0.97 (3H, d, J=7.0), 1.33 (6H, dt, J=5.0, 7.8), 1.37 (3H, s), 1.56 (3H, s), 1.59 (3H, s), 2.75 (1H, ddd, J=1.4, 3.2, 16.0), 2.86 (1H, ddd, J=3.4, 8.0, 16.0), 3.24 (1H, dq, J=7.2, 25.4), 3.64 (3H, s), 4.46 (1H, d, J=5.0), 4.91 (1H, dd, J=5.0, 8.0), 5.04 (1H, t, J=6.0), 5.14 (1H, t, J=6.0), 7.35 (5H, m), 9.75 (1H, dd, J=1.4, 3.4).
19	140~141	+38° (*c* 1.14)	δ 1.02 (3H, d, J=7.0), 1.76 (3H, s), 3.40 (3H, s), 3.69 (3H, s), 4.44 (1H, d, J=12.0), 4.45 (1H, d, J=6.0), 4.66 (1H, d, J=7.0), 4.78 (1H, d, J=6.0), 4.79 (1H, d, J=7.0), 4.82 (1H, d, J=12.0), 4.90 (1H, d, J=1.6), 4.92 (1H, t, J=6.0), 4.92 (1H, t, J=6.2), 5.34 (1H, t, J=8.0), 7.28 (5H, m).
20	Syrup	+65° (*c* 0.93)	δ 1.06 (3H, d, J=7.6), 3.41 (3H, s), 3.54 (2H, br d, J=4.4), 3.85 (1H, dd, J=3.8, 10.6), 4.16 (1H, d, J=5.6), 4.67 (1H, dd, J=5.6, 6.4), 4.90 (1H, d, J=2.0), 4.97 (1H, d, J=8.4), 5.27 (1H, t, J=5.6), 5.48 (1H, t, J=6.4).

Table 1-2. Physico-chemical properties of compounds.

No.	MP (°C)	$[\alpha]_D$ ($CHCl_3$)	^{1}H-NMR (270 or 400 MHz; $CDCl_3$; δ ppm; J Hz)
21	Syrup	+20° (*c* 0.65)	δ 0.88 (3H, s), 1.05 (3H, d, J=7.0), 1.50 (3H, s), 1.58 (3H, s), 1.77 (3H, s), 3.40 (3H, s), 3.70 (1H, d, J=5.0), 4.68 (1H, dd, J=5.0, 7.2), 4.87 (1H, br s), 4.92 (1H, t, J=6.0), 5.33 (1H, t, J=6.4), 6.64 (1H, t, J=7.0), 7.31 (5H, m).
22	Syrup		δ 0.92 (3H, s), 1.06 (3H, d, J=7.2), 1.53 (3H, s), 1.59 (3H, s), 1.61 (3H, s), 3.43 (3H, s), 3.68 (1H, d, J=5.0), 3.97 (1H, dd, J=4.0, 11.6), 4.63 (1H, dd, J=5.0, 7.0), 4.90 (1H, d, J=3.0), 5.00 (1H, m), 5.35 (2H, m), 7.31 (5H, m).
23	Syrup	+26° (*c* 0.25)	δ 1.10 (3H, s), 1.15 (3H, d, J=7.0), 1.63 (6H, s), 1.70 (3H, s), 2.80 (1H, dd, J=10.4, 13.6), 3.67 (1H, br d, J=4.0), 4.09 (1H, dd, J=7.4, 11.0), 4.25 (1H, br s), 4.57 (1H, dd, J=3.2, 11.0), 5.15 (1H, dd, J=3.0, 7.0), 5.30 (1H, dd, J=4.0, 12.2), 5.34 (1H, m), 5.58 (1H, t, J=5.2).

Scheme 3.



Conditions; (a) 1) $NaBH_4$/MeOH, 0°C, 15 minutes 2) MOMCl, DIPEA/$(CH_2Cl)_2$, 60°C, 1 hour; 92% (b) 1) LiOHaq/MeOH, 60°C, 1 hour 2) MeI/HMPA, rt, 30 minutes; 80% (c) TPAP, NMO, MS-4A/CH_2Cl_2, rt, 3 hours; 78% (d) DIPEA, LiCl/CH_3CN, rt, 72 hours; 75% (e) 1) Li-*n*-$BuBH_3$/THF, rt, 0.5 hour 2) TBSOTf, 2,6-lutidine/CH_2Cl_2, 0°C, 1 hour; 78% (f) $LiAlH_4/Et_2O$, 0°C, 15 minutes; 88% (g) 1) PDC, Zeolite/CH_2Cl_2, rt, 2 hours 2) $NH_2NH_2 \cdot H_2O$, NaOH/TEG, 190°C, 2 hours; 65% (h) 1) TBAF/THF, 60°C, 12 hours 2) MnO_2/CH_2Cl_2, rt, 48 hours; 92% (i) (*S*)-BINAL-H/CH_2Cl_2-THF=4:1, −10°C, 1 hour; 90% (j) 1) 2 M HCl/THF, 60°C, 3 hours 2) $NaBH_4$/MeOH, rt, 15 minutes 3) BzCl, Py, DMAP/CH_2Cl_2, rt, 5 hours; 62% (k) $(COCl)_2$, DMSO, Et_3N/CH_2Cl_2, −78°C, 1 hour; 90% (l) 1 M NaOHaq/MeOH, 50°C, 1 hour; 70%.

and allylic hydroxy groups, the major α-alcohol was isolated as the benzoate **23**. Finally, the diol was oxidized to the diketone, which naturally formed the keto-enol structure, and the *O*-benzoyl groups were removed to afford optically active terpestacin (**1**) [FAB-MS *m/z* 403 $(M+H)^+$]. The synthetic (+)-terpestacin (**1**) was identical with the natural product in all respects [MP 172~173°C, $[\alpha]_D$ +26° ($CHCl_3$)][1], completing the first total synthesis of natural terpestacin.

Acknowledgment

We are grateful to Yamanouchi Pharmaceutical Co., Ltd., Shikoku Chemicals Co., Waseda University Grant for Special Research Projects, and High-Tech Research Center Project the Ministry of Education, Science, Sports and Culture, for the generous supports of our program. We also thank Prof. T. OKI, Toyama Prefectural University for kindly providing the natural product, and Mr. T. SATSUKA for his experimental assistance.

KUNIAKI TATSUTA*
NAOYUKI MASUDA

Department of Applied Chemistry,
School of Science and Engineering,
Waseda University,
3-4-1 Ohkubo, Shinjuku, Tokyo 169-0072, Japan

(Received February 27, 1998)

References

1) OKA, M.; A. IIMURA, O. TENMYO, Y. SAWADA, M. SUGAWARA, N. OHKUSA, H. YAMAMOTO, K. KAWANO, S.-L. HU, Y. FUKAGAWA & T. OKI: Terpestacin, a new syncytium formation inhibitor from *Arthrinium* sp. J. Antibiotics 46: 367~373, 1993
2) OKA, M.; S. IIMURA, Y. NARITA, T. FURUMAI, M. KONISHI, T. OKI, Q. GAO & H. KAKISAWA: Stereochemistry and biosynthesis of terpestacin, a new syncytium formation inhibitor. J. Org. Chem. 58: 1875~1881, 1993
3) LIM, C.-H.; H. MIYAGAWA, T. UENO, H. TAKENAKA & T. TSURUSIMA: Isolation and structure elucidation of terpenoid phytotoxins produced by the plant pathogenic fungus *Bipolaris cynodontis*. Abstracts of Papers of 37th Symposium on the Chemistry of Natural Products. pp. 325~330, Tokushima, Japan, 1995
4) TATSUTA, K.; N. MASUDA & H. NISHIDA: The first total synthesis of (±)-terpestacin, HIV syncytium formation inhibitor. Tetrahedron Lett. 39: 83~86, 1998
5) JARGLIS, P. & F. W. LICHTENTHALER: Boron trifluoride-catalyzed oxidation of glycal esters: An effective and mild method for their conversion into α,β-unsaturated lactones. Tetrahedron Lett. 23: 3781~3784, 1982
6) NOYORI, R.; I. TOMINO & Y. TANIMOTO: Vertually complete enantioface differentiation in carbonyl group reduction by a complex aluminum hydride reagent. J. Am. Chem. Soc. 101: 3129~3131, 1979