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The First Total Synthesis of (±)-Terpestacin, HIV Syncytium Formation Inhibitor

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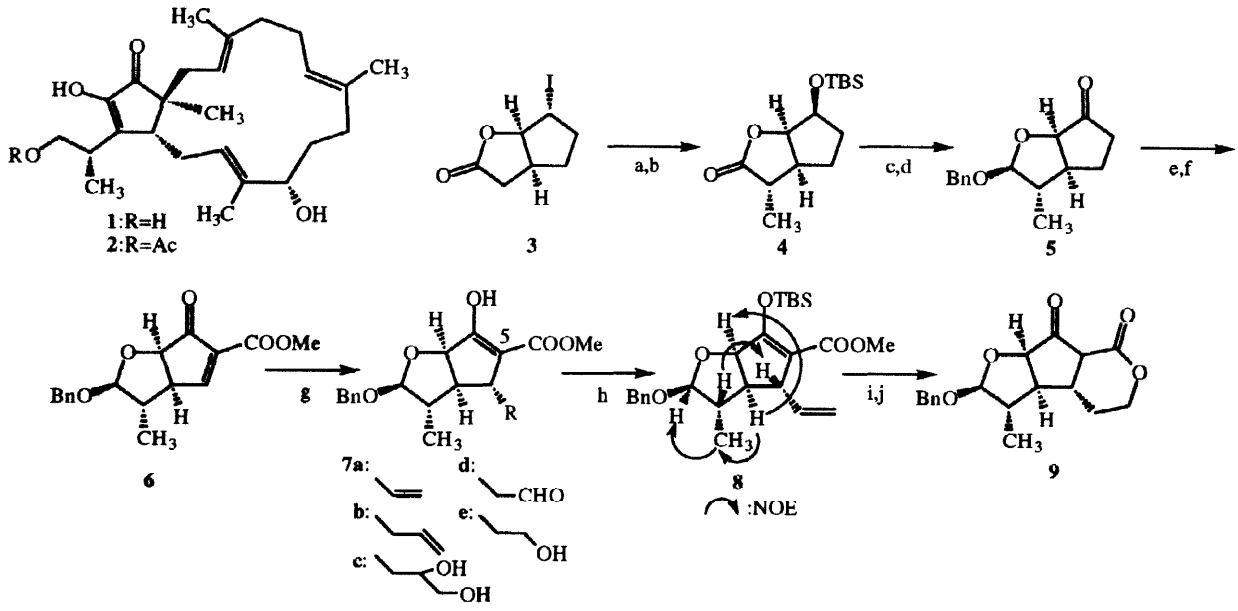
Abstract: (±)-Terpestacin has been synthesized through *C*-alkylation of β-keto lactone **9** with chain portion **12**. These two compounds were derived from 2-cyclopenten-1-ylactic acid and *E,E*-farnesol, respectively.

Terpestacin (**1**) is a bicyclo 5-15-fused sesterterpene isolated from *Arthrinium* sp. metabolites as a novel syncytium formation inhibitor in HIV infection.[1] The absolute structure has been determined by chemical studies and X-ray crystallography.[2] Independently, the same compound has been reported as a phytotoxin from *Bipolaris cynodontis*.[3] The acetate **2** (proliferin) was also isolated as a mycotoxin from *Fusarium proliferatum*.[4] Previous synthetic approaches to terpestacin (**1**) are few, although an elegant model study has been reported by Yoshii's group.[5] We describe here the first total synthesis of (±)-terpestacin (**1**) which solves the problem of establishing the proper relative configurations.



Conditions; (a) 1) 6M NaOHaq,100°C,1h 2)TBSCl,DIPEA / DMF,rt,12h;quant.(b) LDA,MeI / THF,-78°C,0.5h,95%
(c) 1) DIBAL / PhMe,-78°C,1h 2) BnBr,BaO,$Ba(OH)_2$ / DMF,rt,18h 3) TBAF / THF,rt,12h;75% (d) PCC,Zeolite / CH_2Cl_2,rt,3h,90%
(e) LiHMDS,$NCCO_2Me$ / THF,-78°C,1h,92% (f) 1) PhSeCl / EtOAc,rt,30min 2) $NaIO_4$ / THF-H_2O,rt,12h;75%
(g) H_2C=CHMgBr,CuBr-Me_2S,TMSCl / THF,-78°C,15min,90% (h) TBSCl,DIPEA / DMF,rt,5h,quant.
(i) 1) 9-BBN / THF,rt,5h 2) H_2O_2,NaOHaq / THF,-10°C,10min;90% (j) 1) NaH / THF,60°C,3h 2) AcOH-THF-H_2O,60°C,1h;82%

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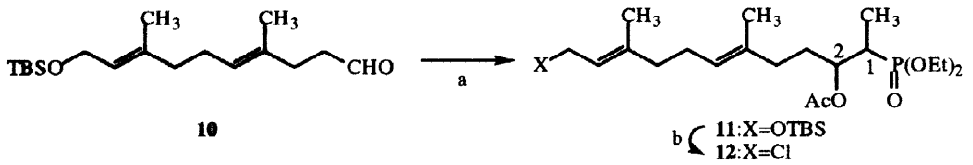
As our first target for their construction, we selected **7a** which we planned to assemble from a bicyclic lactone **3** (oil).[6] The latter resulted from the stereospecific iodo-lactonization of 2-cyclopenten-1-ylacetic acid (~100%: I_2, $NaHCO_3/H_2O$). The relative configuration of **3** was confirmed by the structural determination of **8** later on. This *cis*-fused structure will dictate the creation of all the other required stereocenters in a relative sense. After S_N2-type hydrolysis, the resulting β-alcohol was silylated, followed by treatment with LDA and MeI to provide exclusively the α-methylated compound **4** (oil) resulting from the steric accessibility of the convex face. Hydride reduction and *O*-benzylation of **4** to give the β-*O*-benzyl-lactol, followed by sequential de-*O*-silylation and oxidation, gave preferentially the ketone **5** (mp 71-72°C). This was submitted to carboxylation[7] to provide the enol of the β-keto ester which, upon phenylselenation and periodate oxidation, was converted to the α,β-unsaturated ketone **6** (mp 107-108°C). Michael addition of a vinyl group[8] to **6** was governed by steric factors which favor reaction from the convex site of the bicyclic system. The resulting α-vinyl compound **7a** (oil) was obtained as an enol ester in 90% yield. The relative configuration was determined by NOE studies of the corresponding *O*-silyl ether **8** (oil).

With ready access to multigram quantities of **7a**, an extensive study was then undertaken to establish the optimal conditions for *C*-alkylation at C5 of **7a** (and its analogs **7b-e**) with the following chain portion **12** by using Cs_2CO_3 and CsI. Disappointingly, none of these conditions afforded the desired *C*-alkylated products in high yields, but preferential *O*-alkylation occurred. The main reason for the failure of *C*-alkylation seems to stand in the stable enol-form of **7**. We thought it likely that a potential solution to this problem would be to introduce some strain to the five-membered ring. This could be accomplished by formation of the fused lactone ring such as in **9**. Gratifyingly, hydroboration of **8** followed by lactonization and de-*O*-silylation gave the β-keto lactone **9** (mp 136-137°C) without enol formation.

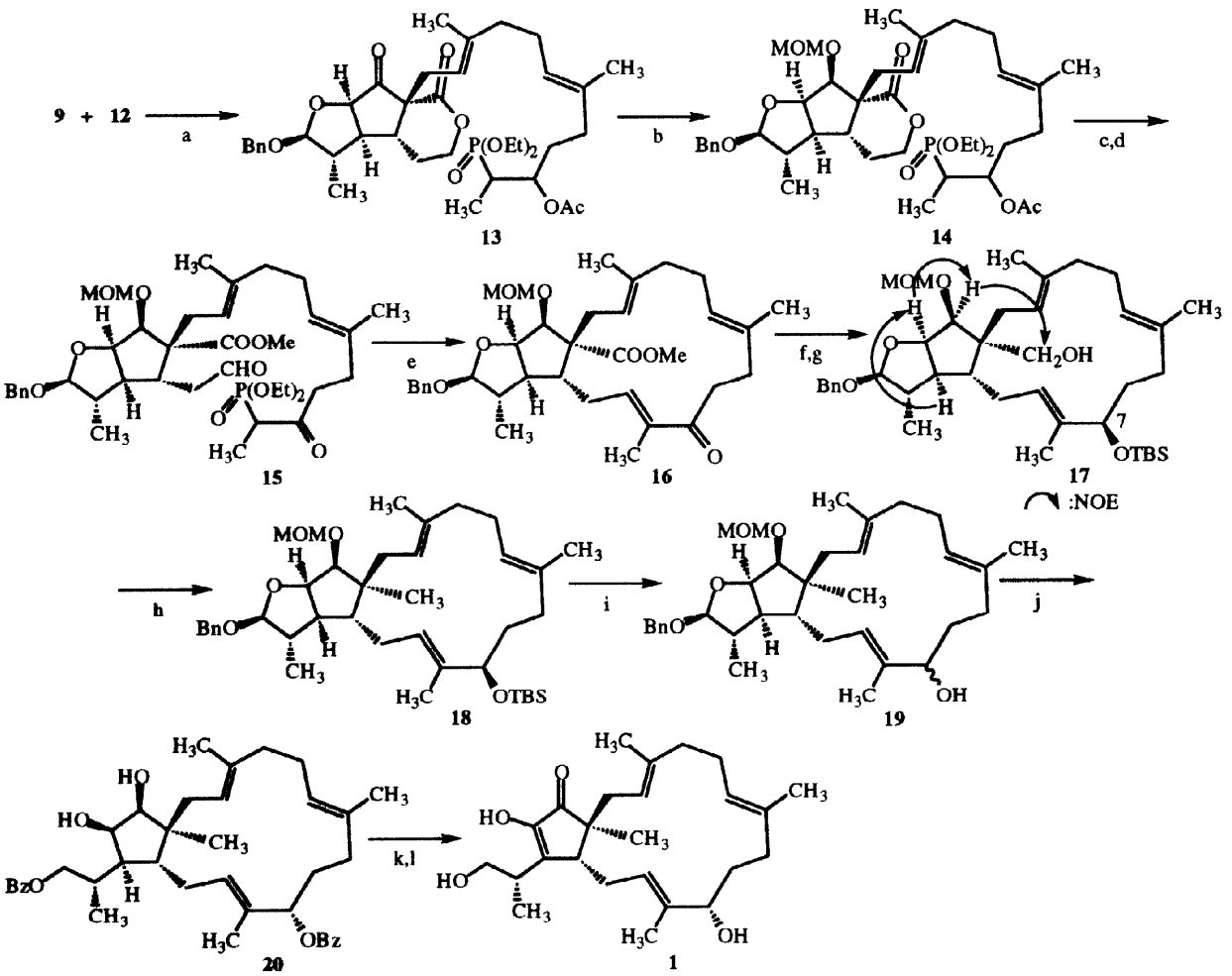
With the biosynthesis[2] of **1** in mind, the chain portion **12** was synthesized from *E,E*-farnesol as follows. Selective ozonolysis of the *O*-silylated farnesol afforded the aldehyde **10** (oil), which was treated with lithiated $EtP(O)(OEt)_2$ followed by acetylation to give a 5 : 1 mixture of **11** (oil). Although both asymmetries at C1 and C2 would disappear on the later stage such as in **15**, only the major product was used for the next step.[9] De-*O*-silylation of **11** followed by chlorination gave the desired phosphonate containing allyl chloride **12** (oil).

We were encouraged to find that, when the β-keto lactone **9** was exposed to the allyl chloride **12** in the presense of Cs_2CO_3 and CsI, a single product **13** (oil) was obtained in 90% yield with less than 1% of *O*-alkylated product. Hydride reduction of **13** to give the β-alcohol followed by methoxymethylation led to **14** (oil). The relative configurations are assigned by the NOE studies of **17**. The lactone **14** was hydrolyzed and esterified to the hydroxy ester, which was oxidized to the keto-aldehyde **15** (oil). Horner-Emmons cyclization of **15** under Masamune's conditions[10] produced the α,β-unsaturated ketone **16** (mp 107-108°C). Hydride reduction of **16** followed by silylation gave the β-*O*-silylated alcohol having an ester group, which was reduced to the primary alcohol **17** (oil). At this stage, the stereochemistry was confirmed mainly by the NOE's as indicated. Although the configuration at C7 was not completely assigned, this seemed to have the unnatural stereochemistry, because **17** could not be directly converted to the natural product. Oxidation of **17** to the aldehyde was followed by Wolff-Kishner reduction to give the *C*-methyl compound **18** (oil). This was converted to a 2:1 mixture of α and β-alcohols **19** (oil) in threee steps: desilylation, oxidation and reduction (82% overall yield). The mixture was hydrolyzed to the lactol, followed by hydride reduction and selective benzoylation to give a diastereomeric mixture of the dibenzoate. The mixture was separated to give the α-benzoate **20** (oil), which could be converted to terpestacin (**1**). Oxidation of **20** was assayed under a variety of

conditions and the best result was realized by Swern oxidation. Finally, de-*O*-benzoylation of the resulting keto enol afforded (±)-terpestacin (**1**: mp 177-178°C; FAB-MS: 403 $[M+H]^+$, 425 $[M+Na]^+$), the NMR[6] and IR (KBr: 1700, 1655 cm^{-1}) spectra of which were identical with those of an authentic sample[11].



Conditions; (a) 1) $(EtO)_2P(O)CH_2CH_3$,n-BuLi / THF,-78°C,1h 2) Ac_2O,DMAP,Py / CH_2Cl_2,rt,5h;85%
(b) 1)TBAF / THF,rt,10h 2) MsCl,LiCl,s-collidine / CH_2Cl_2,rt,3h;85%



Conditions; (a) Cs_2CO_3,CsI / CH_3CN,50°C,3h,90% (b) 1) $NaBH_4$ / MeOH,0°C,15min 2) MOMCl,DIPEA / $(CH_2Cl)_2$,60°C,1h;92%
(c) 1) LiOHaq / MeOH,60°C,1h 2)MeI / HMPA,rt,30min;80% (d) TPAP,NMO,MS-4A / CH_2Cl_2,rt,3h,78%
(e) DIPEA,LiCl / CH_3CN,rt,72h,75% (f) 1) Li-n-$BuBH_3$ / THF,rt,0.5h 2) TBSOTf,2,6-lutidine / CH_2Cl_2,0°C,1h;78%
(g) $LiAlH_4$ / Et_2O,0°C,15min,88% (h) 1) PDC,Zeolite / CH_2Cl_2,rt,2h 2) NH_2NH_2•H_2O,NaOH / TEG,190°C,2h;65%
(i) 1) TBAF / THF,60°C,12h 2) MnO_2 / CH_2Cl_2,rt,48h 3) DIBAL / CH_2Cl_2,rt,15min;80%
(j) 1) 2M HCl / THF,60°C,3h 2) $NaBH_4$ / MeOH,rt,15min 3) BzCl,Py,DMAP / CH_2Cl_2,rt,5h;62%
(k) $(COCl)_2$,DMSO,Et_3N / CH_2Cl_2,-78°C,1h,90% (l) 1M NaOHaq / MeOH,50°C,1h,70%

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6. All compounds were purified by silica-gel column chromatography and/or recrystallization, and were fully characterized by spectroscopic means. Significant ^{1}H-NMR spectral data in $CDCl_3$ (270, 400 and 500 MHz, δ; TMS=0) are the following. **1**: δ 0.98 (3H,s), 1.28 (3H,d,7.2Hz), 4.04(1H, dd, *J*=3.0&10.0 Hz), 5.12 (1H, m), 5.23 (1H, m), 5.39 (1H, m). **3**: δ 2.35 (1H, dd, 2.2&18.6Hz), 2.87 (1H, dd, *J*= 10.3&18.6Hz), 4.46 (1H, d, *J*=4.3Hz), 5.24 (1H, d, *J*= 6.1Hz). **4**: δ 0.10 (6H, s), 0.85 (9H, s), 1.31 (3H, d, *J*=7.7Hz), 4.25 (1H, br t, *J*=3.0Hz). **5**: δ 4.26 (1H, d, *J*= 13.8Hz), 4.32 (1H, d, *J*=8.3 Hz), 4.57 (1H, d, *J*=13.8Hz), 4.83 (1H, s), 7.20-7.35 (5H, m). **6**: δ 3.80 (3H, s), 4.65 (1H, d, *J*=6.0Hz), 8.33 (1H, d, *J*=3.2Hz). **7a**: δ 4.94 (1H, d, *J*=8.0Hz), 5.00 (1H, dd, *J*=2.4&10.4Hz), 5.10 (1H, dd, *J*=2.4&7.4Hz), 5.73 (1H, ddd, *J*=7.4&8.0&10.4Hz), 10.22 (1H, br s). **8**: δ 1.04 (3H, d, *J*=6.8Hz), 2.08 (1H, ddd, *J*=2.8&3.2&10.0Hz), 2.27 (1H, m, 6.8Hz), 3.51 (1H, br d, *J*=8.0Hz), 4.86 (1H, d, *J*=2.0Hz), 4.94 (1H, br d, *J*=10.0Hz). **9**: δ 4.20-4.35 (1H, m), 4.28 (1H, d, *J*=2.0Hz), 4.45-4.53 (1H, m), 4.99 (1H, dd, *J*=2.0&8.4Hz). **10**: δ 2.47 (2H, dt, *J*=3.6&8.4Hz), 4.16 (2H, d, *J*=6.8Hz), 5.12 (1H, dt, *J*=1.2&7.0Hz), 5.27 (1H, dt, *J*=1.2&6.8 Hz), 9.72 (1H, t, *J*=3.6Hz). **11**: δ 1.30 (6H, t, *J*= 6.8Hz), 2.02 (3H, s), 3.99-4.15 (4H, m, *J*=6.8 Hz), 4.98-5.10 (2H, m, *J*=6.0Hz), 5.26 (1H, t, *J*= 6.0Hz). **12**: δ 4.10 (2H, d, *J*=7.0Hz), 5.10 (1H, t, *J*=6.8 Hz), 5.19 (1H, ddd, *J*=4.4&10.0&13.0 Hz), 5.44 (1H, dt, *J*=1.6& 7.0Hz). **13**: δ 1.07 (3H, d, *J*= 7.0Hz), 2.05 (3H, s), 4.79 (1H, s), 4.96 (1H, t, *J*=7.6Hz), 5.03 (1H, t, *J*=6.4Hz), 5.19 (1H, ddd, *J*=4.0&10.0& 18.0Hz). **14**: δ 3.49 (3H, s), 4.19-4.30 (3H, *J*=6.0Hz), 4.55 (1H, dd, *J*=6.0&8.0Hz), 4.84 (1H, d, *J*=6.6Hz), 4.96 (1H, d, *J*=6.6 Hz). **15**: δ 3.24 (1H, dq, *J*=7.2&25.4Hz), 3.64 (3H, s), 9.75 (1H, dd, *J*=1.4&3.4Hz). **16**: δ 4.92 (1H, t, *J*=6.0 Hz), 5.34 (1H, t, *J*=6.2Hz), 6.60 (1H, t, *J*=8.0 Hz). **17**: δ -0.06 (3H, s), 0.00 (3H, s), 0.86 (9H, s), 3.54 (2H, br d, *J*= 4.4Hz), 3.85 (1H, dd, *J*=3.8&10.6Hz), 5.48 (1H, t, *J*=6.4Hz). **18**: δ 0.85 (3H, s), 3.66 (1H, d, *J*=5.0Hz), 3.81 (1H, dd, *J*=4.0&10.2Hz). **19**(α): δ 3.43 (3H, s), 3.96 (1H, 3.6&10.4Hz). (β): δ 3.36 (3H, s), 3.89 (1H, dd, *J*=3.6& 10.4Hz). **20**: δ 4.09 (1H, dd, *J*=7.4&11.0Hz), 4.57 (1H, dd, *J*=3.2&11.0Hz), 5.30 (1H, dd, *J*=4.0&12.2Hz).
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