

Efficient Synthesis of the C1- C7 Fragment of Didemnaketal A

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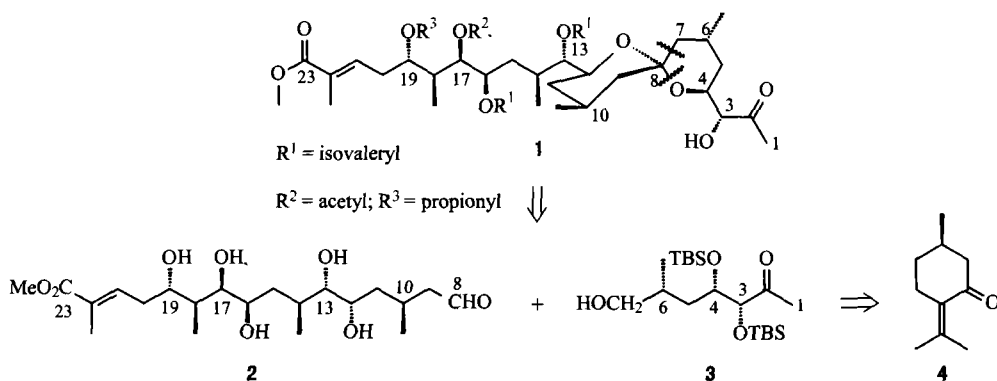
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Abstract: The stereoselective synthesis of the C₁-C₇ fragment (3R,4S,6R)-3,4-di[(*tert*-butyldimethylsilyl)oxy]-7-hydroxy-6-methylheptan-2-one, which is the crucial intermediate for synthesis of the HIV-1 protease inhibitive didemnaketals, was developed *via* 12 steps from the natural (+)-pulegone.

Keywords: Didemnaketals, stereoselective synthesis, intramolecular chiral induction, Mitsunobu reaction.

Didemnaketals A (IC₅₀ = 2 μmol/L) and B (IC₅₀ = 10 μmol/L), as significant inhibitors to HIV-protease¹, were first reported by D. J. Faulkner *et al.* in 1991, and the absolute configurations of them were further determined in this group in 2002². Based on our previous work³, we redesigned and synthesized the C₁-C₇ fragment **3** (3R,4S,6R)-3,4-di-[(*tert*-butyldimethylsilyl)oxy]-7-hydroxy-6-methylheptan-2-one, which is crucial for the synthesis of didemnaketals as shown in the retrosynthetic analysis outlined in **Scheme 1**.

Scheme 1

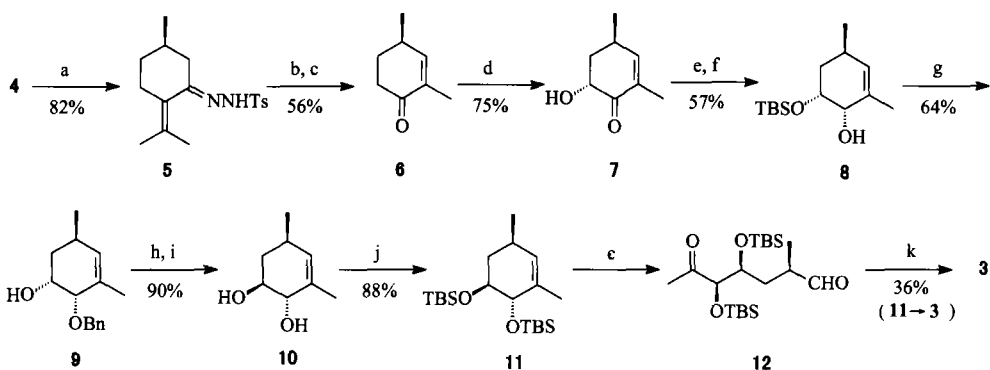


This new approach to the fragment **3** is commenced with the natural (+)-pulegone **4**. The important intermediate enone **6**, which could not be obtained in our earlier primary

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investigation, was conveniently prepared from the precursor **5** through two transformations involving Shapiro coupling with CH_3I and regioselective ozonolysis at -78°C . With enone **6** in hand, compound **9** could be afforded by a series of the intramolecular chiral induction. Following the complete stereochemical inversion of C-1 hydroxy in **9** using Mitsunobu reaction, the construction of all desired stereocenters was efficiently accomplished to give compound **10**, which gave rise to the fragment **3** *via* three steps.

Scheme 2



Reagents and conditions: a) *p*-TsNHNH₂, MeOH, HCl (Cat.); b) i. *n*-BuLi, TMEDA, -78°C ; ii. MeI, 0°C ; c) O₃, CH₂Cl₂, -78°C ; d) i. LDA, TMSCl, -78°C ; ii. *m*-CPBA, NaHCO₃, CH₂Cl₂, -20°C ; iii. (*n*-Bu)₄NF, THF; e) TBSCl, imidazole, DMF; f) NaBH₄, MeOH, -20°C ; g) i. BnBr, NaH, DMF, (*n*-Bu)₄NI (Cat.); ii. (*n*-Bu)₄NF, THF; h) i. *p*-NO₂C₆H₄CO₂H, PPh₃, DEAD, C₆H₆; ii. MeOH, KOH, H₂O; i) *t*-BuNH₂, K, THF; j) TBSCl, imidazole, DMF, 50°C ; k) NaBH₄, EtOH/CH₂Cl₂ (3:7).

Acknowledgments

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References and Notes

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- Compound **3**: $[\alpha]_D^{25} = -10$ (c 1.5, CHCl₃); ¹H NMR (200 M Hz, CDCl₃, δ ppm) : 4.09 (d, 1H, *J* = 3.6 Hz, H-3), 3.94-3.92 (m, 1H, H-4), 3.42 (dd, 2H, *J* = 5.1, 5.8 Hz, OCH₂), 2.20 (s, 3H, H-1), 1.73-0.80 (m, 4H, OH, H-5, and H-6), 0.94 (s, 9H, C(CH₃)₃), 0.92 (d, 3H, *J* = 4.0 Hz, CH₃), 0.90 (s, 9H, C(CH₃)₃), 0.09 (s, 3H, SiCH₃), 0.07 (s, 3H, SiCH₃), 0.06 (s, 3H, SiCH₃), 0.04 (s, 3H, SiCH₃); ¹³C NMR (100 M Hz, CDCl₃, δ ppm) : 210.7, 80.6, 73.6, 68.1, 37.9, 32.0, 28.3, 25.8 (6C), 18.2, 18.0, 17.4, -4.4, -4.7, -4.8, -5.1; FAB-MS *m/z* (%): 405 (M⁺+1, 5), 387 (80), 347 (24), 245 (14), 215 (100), 115 (100). HRMS (ESI): calcd. for C₂₀H₄₄Si₂O₄Na (M+Na) 427.2670, found 427.2673.

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