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Efficient Synthesis of the C1- C7 Fragment of Didemnaketal A

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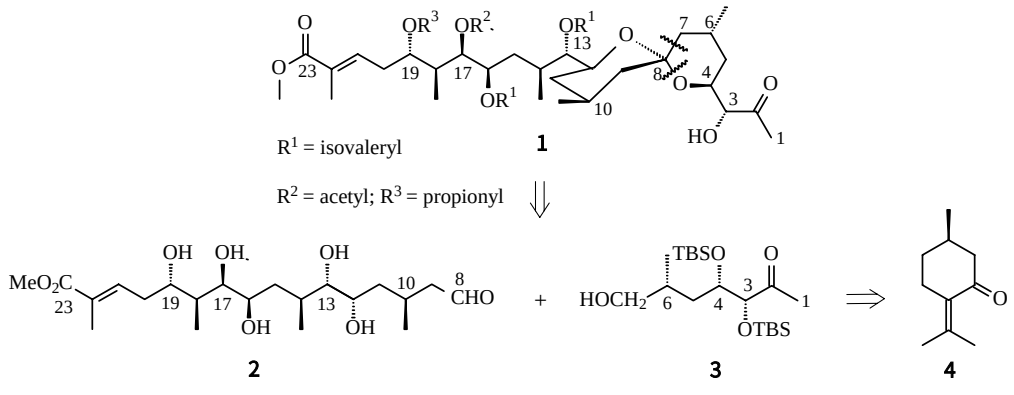
Abstract: The stereoselective synthesis of the C_1-C_7 fragment (3R,4S,6R)-3,4-di[(*tert*-butyl-dimethylsilyl)oxy]-7-hydroxy-6-methylheptan-2-one, which is the crucial intermediate for synthesis of the HIV-1 protease inhibitive didemnaketals, was developed *via* 12 steps from the natural (+)-pulegone.

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

Didemnaketals A (IC_{50} = 2 μmol/L) and B (IC_{50} = 10 μmol/L), as significant inhibitors to HIV-protease[1], were first reported by D. J. Faulkner *et al.* in 1991, and the absolute configurations of them were further determined in this group in 2002[2]. Based on our previous work[3], we redesigned and synthesized the C_1-C_7 fragment **3** (3*R*,4*S*,6*R*)-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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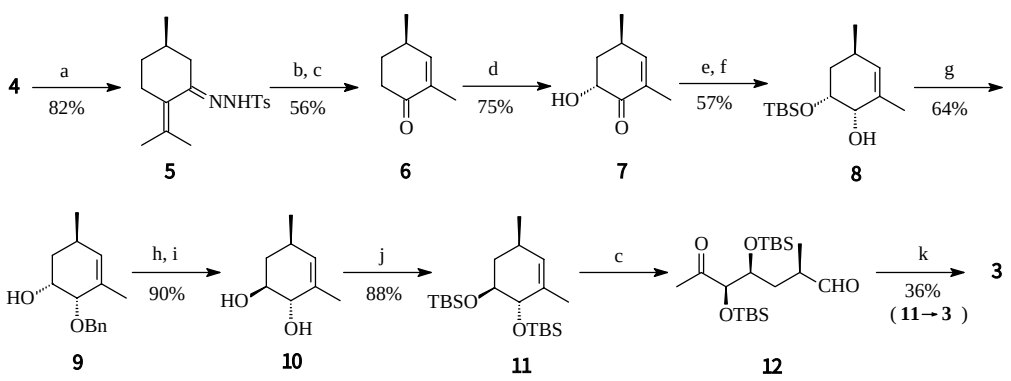
investigation, was conveniently prepared from the precursor **5** through two transformations involving Shapiro coupling with CH_3I and regioselective ozonolysis at -78°C[4]. With enone **6** in hand, compound **9** could be afforded by a series of the intramolecular chiral induction. Following the complete 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*-$TsNHNH_2$, MeOH, HCl (Cat.); b) i. *n*-BuLi, TMEDA, -78°C; ii. MeI, 0°C; c) O_3, CH_2Cl_2, -78°C; d) i. LDA, TMSCl, -78°C; ii. *m*-CPBA, $NaHCO_3$, CH_2Cl_2, -20°C; iii. $(n\text{-}Bu)_4NF$, THF; e) TBSCl, imidazole, DMF; f) $NaBH_4$, MeOH, -20°C; g) i. BnBr, NaH, DMF, $(n\text{-}Bu)_4NI$(Cat.); ii. $(n\text{-}Bu)_4NF$, THF; h) i. *p*-$NO_2C_6H_5CO_2H$, PPh_3, DEAD, C_6H_6; ii. MeOH, KOH, H_2O; i) *t*-$BuNH_2$, K, THF; j) TBSCl, imidazole, DMF, 50°C; k) $NaBH_4$, $EtOH/CH_2Cl_2$ (3:7).

Acknowledgments

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References and Notes

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5. Compound **3:** $[\alpha]_D^{25}$ = -10 (*c* 1.5, $CHCl_3$); ^1H NMR (200 M Hz, $CDCl_3$, 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, OCH_2), 2.20 (s, 3H, H-1), 1.73-0.80 (m, 4H, OH, H-5, and H-6), 0.94 (s, 9H, $C(CH_3)_3$), 0.92 (d, 3H, *J* = 4.0 Hz, CH_3), 0.90 (s, 9H, $C(CH_3)_3$), 0.09 (s, 3H, $SiCH_3$), 0.07 (s, 3H, $SiCH_3$), 0.06 (s, 3H, $SiCH_3$), 0.04 (s, 3H, $SiCH_3$); ^{13}C NMR (100 M Hz, $CDCl_3$, 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 $C_{20}H_{44}Si_2O_4Na$ (M+Na) 427.2670, found 427.2673.

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