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Synthetic studies of the HIV-1 protease inhibitive didemnaketals: precise and stereocontrolled synthesis of the key mother spiroketal

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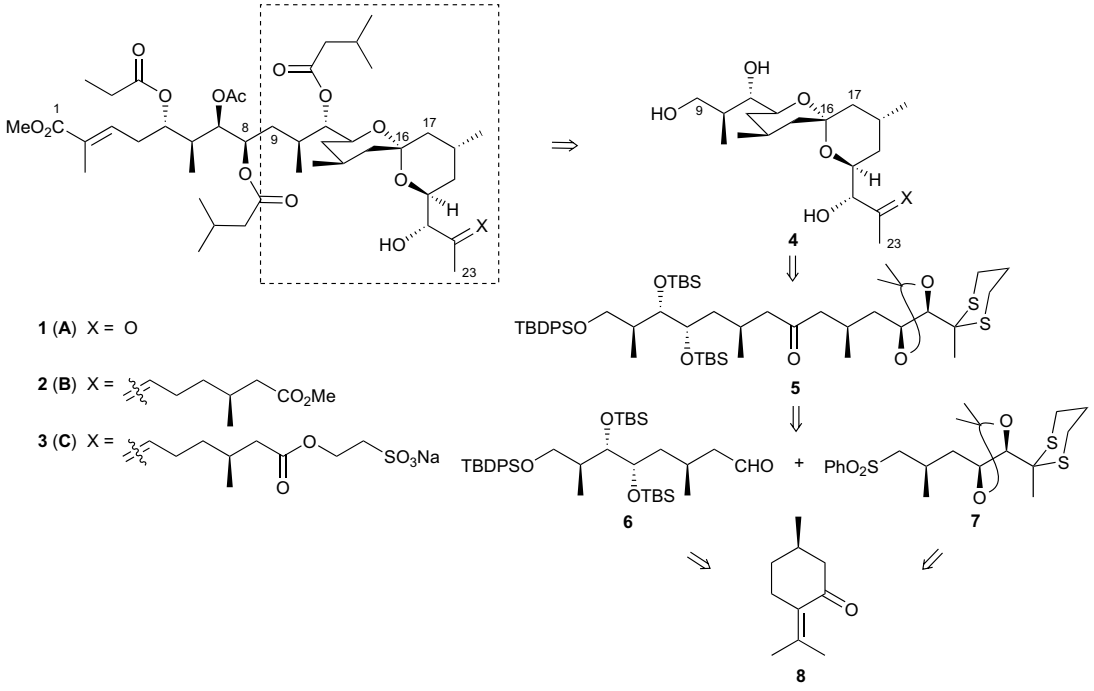
Abstract—The precise and stereocontrolled synthesis of the C_9–C_{23} portion, the key mother spiroketal of the HIV-1 protease inhibitive didemnaketals from the ascidian *Didemnum* sp., has been carried out through multisteps starting from (*R*)-pulegone as the chiral template. This approach involved the distereoselective construction of eight chiral centers by intramolecular chiral inducement and the coupling of two fragments by Julia reaction.

Didemnaketals **A** (**1**) and **B** (**2**) (Scheme 1) were isolated by Faulkner and co-workers from the ascidian *Didemnum* in 1991 and exhibited to be highly inhibitive to HIV-1 protease with the IC_{50} being 2 and 10 μM, respectively.[1]



Scheme 1. Didemnaketal **A**, **B**, **C** and retrosynthesis of the C_9–C_{23} spiroketal portion.

Keywords: Key mother spiroketal; HIV-1 protease; Intramolecular chiral inducement; Julia reaction.
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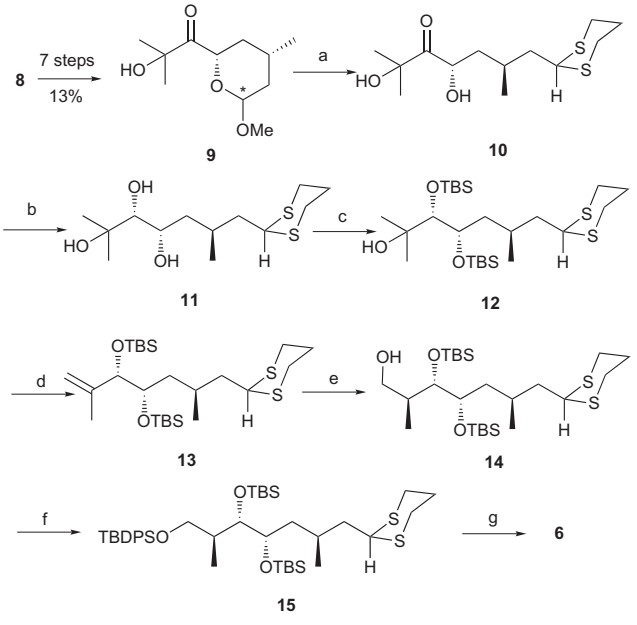
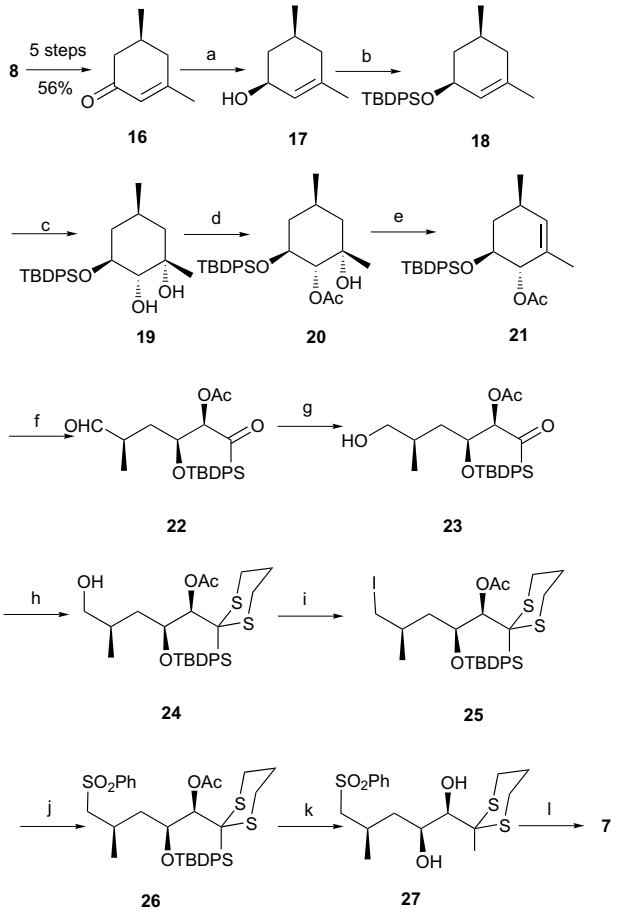
Previously, we had designed and synthesized their spiroketals portion vaguely.[2] However in 2002, Faulkner and co-workers modified and finished the full relative and absolute stereochemistry of the didemnaketals,[3] which makes us design another asymmetric total synthesis of this kind of compounds. Recently, we performed the precise synthesis of the ester side-chain (the C_1–C_8 portion).[4] Here, we present our stereocontrolled synthesis of the C_9 to C_{23} spiroketal portion **4** of the didemnaketals, which have eight precise stereocenters (10*S*,11*S*,12*S*,14*S*,16*S*,18*R*,20*S*,21*S*).

Our synthesis, shown in the retrosynthetic analysis (Scheme 1), was based on the selection of (*R*)-pulegone **8** as a starting material, as its (*R*)-Me could generate a series of conjoint stereocenters in compound **6** (C_{10}–C_{12}) and **7** (C_{20}–C_{21}). Aldehyde **6** and sulfone **7** could be coupled by Julia reaction and then ketone **5** would be prepared, which could be spiroketalized to the key mother spiroketal **4**.

Firstly, we prepare the acetal **9** in two isomers (1/1) from (*R*)-pulegone **8** with 13% yield through seven steps.[2] The transacetalization of **9** with 1,3-thiopropanol produced α-hydroxyl ketone **10**. The α-hydroxyl ketone **10** was reduced to triol **11** with 82% de value and 85% yield by DIBAL-H.[5] Selective protection of two secondary hydroxyl groups in **11** with TBSCl to afford alcohol **12**, which upon dehydration of the tertiary hydroxyl group, gave the compound **13** with the terminal double bond. Subsequently, diastereoselective hydroboration of the double bond in compound **13** with 9-BBN[6] followed by oxidative workup afforded the hydroxyl compound **14** in which the three conjoint sterecenters were constructed successfully. The subsequent protection of the



Scheme 2. Reagents and conditions: (a) $CH_2(CH_2SH)_2$, $BF_3{\cdot}Et_2O$, CH_2Cl_2, 0 °C, 53%; (b) DIBAL-H, THF, −78 °C, 85%; (c) TBSCl, imid., DMF, 90 °C, 78%; (d) $SOCl_2$, Py, 0 °C, 76%; (e) (i) 9-BBN, THF, −78 °C; (ii) H_2O_2, NaOH, 0 °C, 82% (two steps); (f) TBDPSCl, imid., DMF, rt, 95%; (g) NBS, acetone, rt, 67%.



Scheme 3. Reagents and conditions: (a) $NaBH_4$, $CeCl_3{\cdot}7H_2O$, MeOH, 0 °C, 87%; (b) TBDPSCl, imid., DMF, rt, 95%; (c) $K_2OsO_4{\cdot}H_2O$, NMO, ^{t}BuOH–acetone–H_2O (1:2:1), 86%; (d) Ac_2O, DMAP, Py, rt, 97%; (e) $SOCl_2$, Py, 0 °C, 98%; (f) O_3, CH_2Cl_2, −78 °C, 78%; (g) $KBH(OAc)_3$, PhH, rt, 82%; (h) $CH_2(CH_2SH)_2$, $BF_3{\cdot}Et_2O$, CH_2Cl_2, 0 °C, 78%; (i) I_2, imid., PPh_3, $PhCH_3$, 0 °C, 81%; (j) $PhSO_2Na$, DMF, rt, 93%; (k) KOH, H_2O, MeOH, reflux; (l) DMP, TsOH, rt, 90% (two steps).

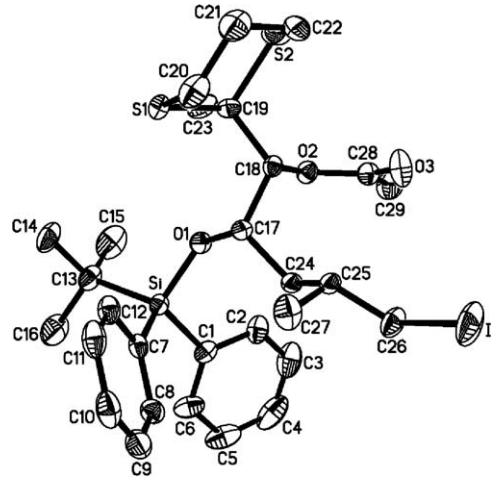
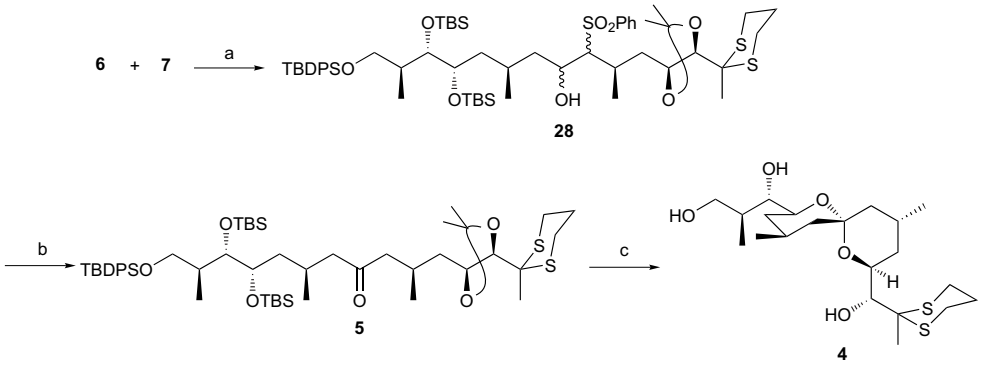


Figure 1. Crystal structure of compound **25**.



Scheme 4. Reagents and conditions: (a) ^{n}BuLi, THF, −78 °C, then **6**, THF, −78 °C, 75%; (b) (i) CrO_3, Py, CH_2Cl_2, 0 °C, 74%; (ii) Na–Hg, MeOH, NaH_2PO_4, rt, 63%; (c) HF (40%), CH_3CN, rt, 35%.

hydroxyl group and deacetalization generated the aldehyde **6** as a C_9–C_{16} fragment of didemnaketals (Scheme 2).

Then, we turned to the construction of C_{17}–C_{23} fragment of didemnaketals (Scheme 3). Conjugative ketone **16** was prepared from (*R*)-pulegone **8** in 56% yield through five steps.[2] Reduction of ketone **16** with $NaBH_4$ followed by protection of the formed hydroxyl group with TBDPSCl afforded alkene **18**. Then, the diol **19** was produced through the stereoselective osmylation[7] of the double bond in compound **18**. Subsequently, selective protection of the secondary hydroxyl group in the diol **19** afforded the intermediate **20**. Fortunately, elimination of the tertiary hydroxyl group in **20**, gave compound **21** with the double bond in six-membered ring (no other isomer was found). Ozonolysis of **21** produced the open-chain keto-aldehyde **22**. Selective reduction of the aldehyde group in **22** followed by thioacetalylation and iodination with iodine afforded the iodide **25**, whose absolute stereochemistry was conformed by X-ray (Fig. 1). This iodide **25** was converted to the sulfone **26** and deprotection of **26** produced the diol **27**. Protection of the diol **27** with DMP afforded the sulfone **7** as a C_{17}–C_{23} fragment of didemnaketals.

The coupling of **6** and **7** was carried out as shown in Scheme 4. Deprotonation of the sulfone **6** with *n*-BuLi and subsequent reaction with aldehyde **7** afforded the α-hydroxy sulfone **28**. Subsequently, oxidation of the hydroxyl group of **28** with Collins reagent[8] and then removal of the sulfone with 6% sodium amalgam gave compound **5** a single isomer as the open-chain polyhydroxyl ketone intermediate **5**. Deprotection of the hydroxyl groups with hydrofluoric acid triggered deprotection and subsequent spirocyclization to afford the final spiroketal **4** as the single product.[9] Thus, we have succeeded in the stereocontrolled synthesis of the key mother spiroketal C_9–C_{23} portion of the HIV-1 protease inhibitive didemnaketals, in which the eight stereocenters (10*S*,11*S*,12*S*,14*S*,16*S*,18*R*,20*S*, and 21*S*) were constructed successfully. Further, study toward total synthesis of the didemnaketals is ongoing in our group.

Acknowledgments

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2005.07.167.

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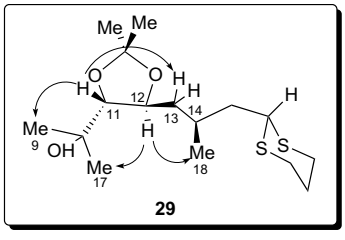
5. The configuration of **11** was determined from its acetonide derivative **29**. The stereochemistry of **29** was conformed through ^{1}H NMR NOE experiment as shown below. For example, irradiation of C_{11}–H (δ: 3.73 ppm) lead to 5% enhancement of C_9–H (δ: 1.33 ppm), and 4% enhancement of C_{13}–H (δ: 1.57 ppm), and irradiation of C_{12}–H (δ: 3.47 ppm) lead to 5% enhancement of C_{17}–H (δ: 1.25 ppm), and 3% enhancement of C_{18}–H (δ: 1.00 ppm).



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9. The analytical data of the compound **4**: $[\alpha]_D^{17}$ +32.0 (*c* 0.2, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ: 4.55 (dd, 1H, $J = 1.6$, 9.6 Hz), 4.07 (dd, 1H, $J = 2.8$, 12.4 Hz), 3.74–3.66 (m, 3H), 3.66 (dd, 1H, $J = 3.2$, 11.2 Hz), 2.94–2.86 (m, 2H), 2.83 (dd, 1H, $J = 3.6$, 8.4 Hz), 2.80–2.74 (m, 2H), 2.10–2.04 (m, 2H), 2.01–1.92 (m, 4H), 1.70 (s, 3H), 1.52–1.47 (m, 3H), 1.31–1.28 (m, 1H), 1.24 (d, 3H, $J = 6.8$ Hz), 1.15–1.09 (m, 1H), 1.04–0.94 (m, 1H), 0.88 (d, 3H, $J = 6.4$ Hz), 0.84 (d, 3H, $J = 7.2$ Hz); ^{13}C NMR (100 MHz) δ: 99.2, 78.6, 76.4, 71.2, 68.3, 63.3, 53.8, 44.3, 40.2, 36.1, 35.1, 30.7, 26.2, 26.1, 25.0, 24.8, 24.5, 24.0, 22.2, 20.7, 13.6; FAB-MS $(M+Li)^+$: *m*/*z* 441; $(M+Na)^+$: *m*/*z* 457; HR-ESIMS: *m*/*z* calcd for $C_{21}H_{38}S_2O_5Na$ (M+Na) 457.2053; found 457.2065.