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Synthetic studies of the HIV-1 protease inhibitive didemnaketals: stereocontrolled synthesis of an ester side chain ☆

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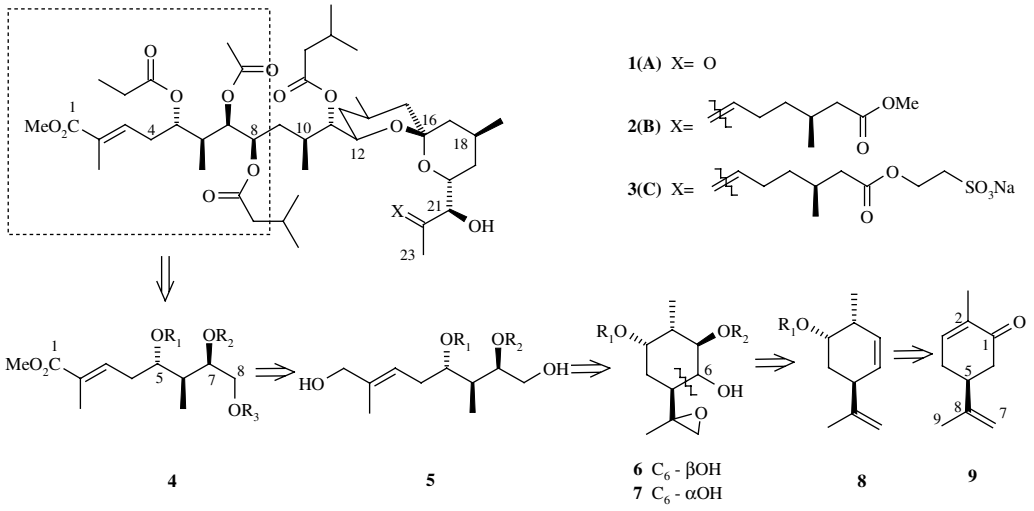
Abstract—The stereocontrolled synthesis of the C_1–C_8 portion, the ester side chain of the HIV-1 protease inhibitive didemnaketals from the ascidian *Didemnum* sp., has been carried out through 15 steps starting from (*S*)-carvone as the chiral template. This approach involved the diastereoselective construction of three conjoint chiral centers by intramolecular chiral inducement, and generation of allylic alcohol intermediate through a key Grob fragmentation reaction.

In 1991, Faulkner and co-workers reported the novel didemnaketals **A** (**1**) and **B** (**2**) (Scheme 1) isolated from the ascidian *Didemnum* sp. at Auluptagel Island, Palau, and demonstrated **A** and **B** exhibited to be highly inhibitive to HIV-1 protease with the IC_{50} being 2 and 10 μM, respectively.[1] In-depth investigation proved the ester side chain might be the main activity portion of the HIV-1 protease didemnaketals.[2] As their important biological activity and particular structure, we have already performed the synthesis of the spiroketal moiety.[3] In 2002, Faulkner and co-workers finished the full assignment of relative and absolute stereochemistry of the didemnaketals,[1c] which benefits our further studies on the asymmetric total synthesis of this kind of compounds. Here, we present our efficient and stereocontrolled synthetic of C_1–C_8 side-chain **4** of the didemnaketals, which have three conjoint stereocenters (C_5–C_7) and the conjugated unsaturated ester.



Scheme 1.

Keywords: Ester side chain; HIV-1 protease; Intramolecular chiral inducement; Grob fragmentation reaction.
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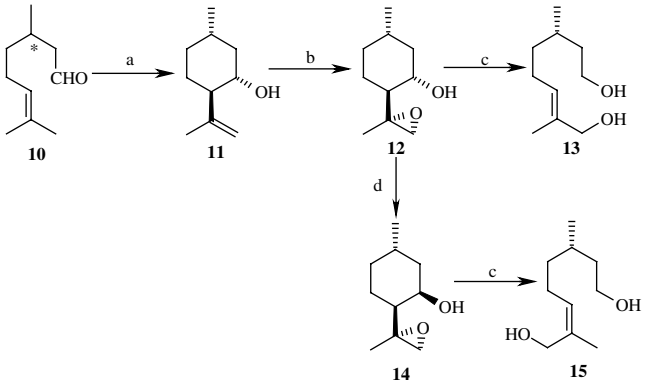
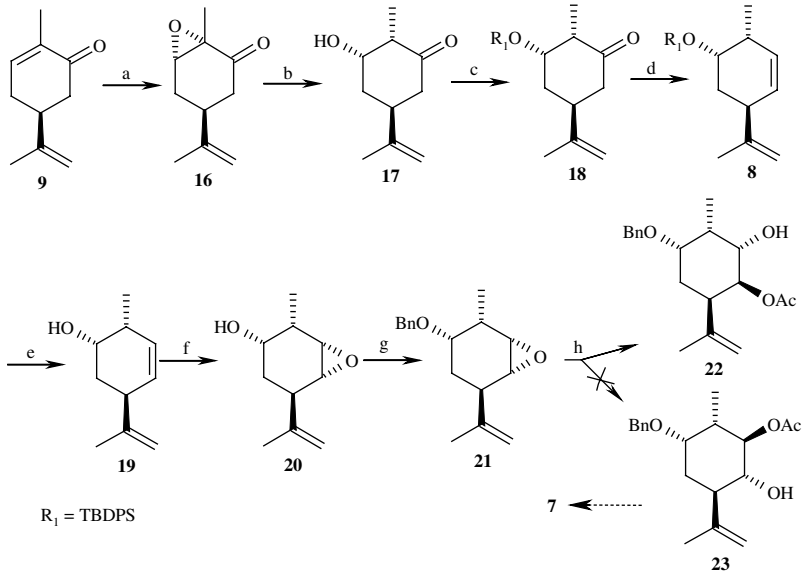
Our synthesis, shown in the retrosynthetic analysis (Scheme 1), was based on the selection of the menthane kind of monoterpene (*S*)-carvone **9** as starting material, for its C_1–carbonyl, C_2–Me, and the isopropene (C_7–C_9) could generate the corresponding C_7–OH, C_6–Me, and the terminal isopropyl ester of **4**, respectively. So a C_6–hydroxy epoxide intermediate **6** (or **7**) was designed and a key Grob fragmentation would be used to generate the open-chained allylic alcohol **5**.[4]

In the initial investigation on the possibility of above synthetic analysis, we tested the key Grob fragmentation using the model substrate **12** prepared from (±)-citronellal **10**.[5] It was very interesting that we observed the configuration of the double bond formed in Grob fragmentation of the epoxide **12** was highly dependent upon the inducement of its OH group. As shown in Scheme 2, if fragmentation of the epoxide **12** bearing the *trans*-OH and epoxyisopropyl located at the six-membered ring (prepared from **11** via direct *m*-CPBA epoxidation) was promoted with Al(^{i}PrO)$_3$, only (*E*)-8-hydroxycitronellol **13** was produced.[6] However, if the substrate **14** possessed the *cis*-OH and epoxyisopropyl (prepared from **12** via Mitsunobu reaction), a (*Z*)-8-hydroxycitronellol **15** was obtained as a single product. This important fact provided alternative procedure for synthesis of the hard-to-available *Z*-double bond, and here suggested that the intermediates **7** could be a favorable precursor for constructing the side-chain **4** with *E*-double bond by use of Grob fragmentation.

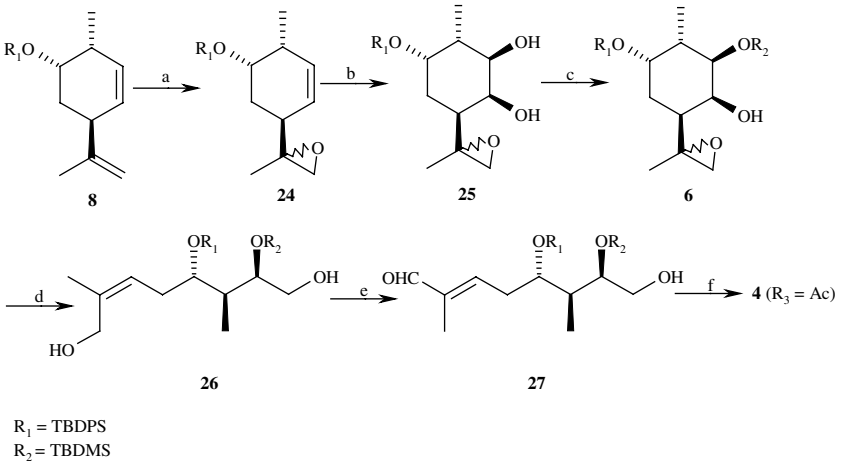


Scheme 2. Reagents and conditions: (a) $ZnBr_2$, CH_2Cl_2, 90%; (b) *m*-CPBA, CH_2Cl_2; 0 °C, 92%; (c) Al(^{i}PrO)$_3$, ^{i}PrOH, reflux, 90%; (d) (i) *p*-$NO_2C_6H_4CO_2H$, PPh_3, DEAD, benzene; (ii) K_2CO_3, MeOH, 72% (2 steps).

On the basis of above model testing, the key intermediate **7** was designed firstly. The synthesis began with the stereoselective epoxidation of commercially available (*S*)-(+)-carvone (**9**) using basic hydrogen peroxide[7] (Scheme 3). Successive organoselenium-mediated catalytic reductive ring opening of the resulting oxirane **16** led to the α-hydroxyl ketone **17**.[8] Therefore the corresponding C_5–OH of **4** was stereoselectively introduced. As the direct protection of C_3–OH in **17** with TBDPSCl led to substantial elimination to give the starting carvone **9**, protection of the C_3–OH had to be performed and the product **18** was obtained in three steps: protecting the carbonyl group in **17** with ethylene glycol, then protecting the hydroxyl group with TBDPSCl and again releasing carbonyl group with TsOH. Subsequently elimination of the carbonyl of **18** by hydrazonization with $TsNHNH_2$ followed by treatment the formed hydrazone with *n*-BuLi afforded diene **8**. With **8** in hand we turned our attention to gain the key intermediate **23**. Thus deprotection of TBDPS of **8** with TBAF followed by stereoselective epoxidation of the formed homoallylic alcohol **19** with TBHP through the inducement of the hydroxyl group and then protection of the hydroxy in **20** afforded the epoxide **21**. Here, the



Scheme 3. Reagnets and conditions: (a) H_2O_2, NaOH, MeOH, 95%; (b) $(PhSe)_2$, *N*-acetylcysteine, NaOH, MeOH, 70%; (c) (i) $(CH_2OH)_2$, PPTS, benzene, reflux; (ii) TBDPSCl, NaH, THF, 0 °C; (iii) TsOH, acetone, 72% (three steps); (d) (i) $TsNHNH_2$, MeOH; (ii) *n*-BuLi, THF, −78 °C, rt, 52% (2 steps); (e) TBAF, THF, reflux, 84%; (f) *t*-BuO_2H, $V(acac)_2$, 89%; (g) BnBr, NaH, TBAI, THF, 0 °C, 68%; (h) HOAc, NaOAc, reflux, 72%.



Scheme 4. Reagents and conditions: (a) *m*-CPBA, CH_2Cl_2, 0 °C, 65%; (b) K_2OsO_4, NMO, ^{t}BuOH–acetone–H_2O (1:2:1) 75%; (c) TBSCl, imid., DMF, 75%; (d) Al(^{i}PrO)$_3$, ^{i}PrOH, 72%; (e) SeO_2, EtOH (95%), reflux, 72%; (f) (i) Ac_2O, DMAP, Py; (ii) $NaClO_2$, 2-methyl-2-butene, NaH_2PO_4, ^{i}BuOH/H_2O; (iii) CH_2N_2, Et_2O, 70% (three steps).

deprotection of TBDPS group in **8** was necessary for the regioselective monoepoxidation of **19** because a direct epoxidation of **8** without inducement of C_3–OH only gave a terminal epoxy product. Unfortunately, the following ring opening of the epoxide **21** with NaOAc could not afford the desired homoallylic alcohol **23** (which could be easily converted to the key intermediate **7**) but the alcohol **22**, which had two opposite stereocenters C_1 and C_6 to **23** and was of no use to our synthesis. The possible reason for this result would be that the diaxial transition state for yielding **22** is more stable than the diequatorial one, which lead to the product **23**.[9]

Subsequently we had to modify the above route for first demanding the desired C_7 stereochemistry of **4** ($R_3 = Ac$). A viable route as shown in Scheme 4 was performed by regioselective epoxidation of the diene **8** with *m*-CPBA and the terminal epoxide **24** in two isomers (1:1) was obtained. Then the stereoselective osmylation[10] of the epoxide **24** followed by selective protection of the equatorial hydroxyl group in the formed diol **25** afforded the intermediate **6**, in which three desired stereocenters corresponding C_5–C_7 have been constructed successfully. Then fragmentation of epoxide alcohol **6** with Al(^{i}PrO)$_3$ afforded the *Z*-allylic alcohol **26**, whose stereochemistry for the double bond and three stereocenters was confirmed through spectroscopy inspection of its derivatives and the configuration of the double bond was just what we anticipated before.[11] The formation of only one isomer of **26** from two isomers of **6** indicated that the configuration of epoxide has no effect on the Grob fragmentation reaction. Fortunately, the following selective oxidation of the *Z*-primary allylic alcohol **26** with selenium (IV) oxide afforded the *E*-unsaturated aldehyde **27** in 70% yield.[12] Protection of the hydroxyl group in the aldehyde **27** with acetic anhydride followed by oxidation of the formed aldehyde with sodium chlorite and then esterification of the formed acid with CH_2N_2 afforded the methyl ester **4** ($R_3 = Ac$) successively.[13] Further total synthetic studies on the didemnaketals are ongoing in our group.

Acknowledgements

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References and notes

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6. The configuration of the double bond in the compound **4**, **13**, **15**, **26**, **27** was confirmed through ^{1}H NMR NOE experiment.
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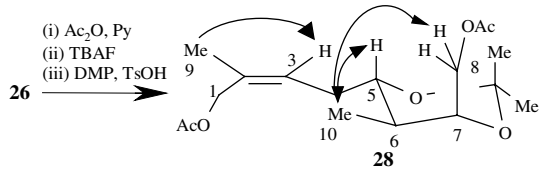
11. The compound **26** was first made into derivative **28** through three steps, and the stereochemistry of **28** was confirmed through ^{1}H NMR NOE experiment and NOESY experiment as shown below. For example, irradiation of C_9–H (δ: 1.76 ppm) lead to 4% enhancement of C_3–H (δ: 5.48 ppm), irradiation of C_5–H (δ: 3.28 ppm) lead to 5% enhancement of C_{10}–H (δ: 0.86 ppm), and irradiation of

C_{10}–H (δ: 0.86 ppm) lead to 4% enhancement of C_5–H (δ: 3.28 ppm) and 4% enhancement of C_8–H (δ: 4.05 ppm)



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13. Analytical data of the compound **4**: ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.66–7.62 (m, 4H), 7.44–7.32 (m, 6H), 6.71 (t, 1H, $J = 6.7$ Hz), 3.90–3.75 (m, 4H), 3.67 (s, 3H), 2.37–2.27 (m, 2H), 1.93 (s, 3H), 1.87–1.83 (m, 1H), 1.65 (s, 3H), 1.04 (s, 9H), 0.95 (d, 3H, $J = 7.2$ Hz), 0.82 (s, 9H), −0.01 (s, 3H), −0.08 (s, 3H); ^{13}C NMR (75 MHz): δ 170.6, 168.3, 139.9, 136.0 (4C), 133.9, 133.8, 129.7 (2C), 128.4, 127.6 (2C), 127.5 (2C), 74.6, 71.7, 67.0, 51.5, 42.5, 32.9, 27.0 (3C), 25.8 (3C), 20.8, 19.3, 18.1, 12.5, 10.0, −4.3, −4.6; FAB-MS $(M+H)^+$, m/z 627; HR-SIMS: m/z calcd for $C_{35}H_{55}Si_2O_6$ (M+H) 627.3532; found 627.3523.