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Synthetic Studies of the HIV-1 Protease Inhibitive Didemnaketals: Stereocontrolled Synthetic Approach to the Key Mother Spiroketals

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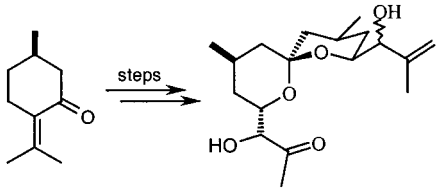
ABSTRACT



The stereocontrolled synthesis of (2*S*,4*R*,6*R*,8*S*,10*S*,1′*R*,1″*R*)-2(acetylhydroxymethyl)-4,10-dimethyl-8(isopropenylhydroxymethyl)-1,7-dioxaspiro[5,5]-undecane (4a) and its C1″-epimer (4b), the key mother spiroketals of the HIV-1 protease inhibitive didemnaketals from the ascidian *Didemnum* sp., has been carried out through multisteps from the natural (*R*)-(+)-pulegone, which involved the diastereoselective construction of four chiral carbon centers(C-2, C-6, C-8, and C-1′) by intramolecular chiral induce.

The didemnaketals isolated from the ascidian *Didemnum* sp. belong to a new kind of complex natural products incorporating the main mother spiroketals **4a** or **4b** and one or two side chains bearing polyacyloxys. Some of the didemnaketals have been proven to be highly inhibitive to HIV-1 protease,[1] but their synthesis has not been reported up to the present. In connection with our study on this subject, a recent effort is focused on the development of the efficient synthetic approach of this kind of compounds and the analogues for the purpose of further investigation of their biological activity. Here, we present our successful synthesis of the key mother spiroketals **4a** and **4b**.

Due to the indetermination of absolute stereochemistry of didemnaketals, we first designed and synthesized the target molecules **4a**/**4b**, whose absolute stereochemistry is indicated in Scheme 1, which would be the same as didemnaketals or their enantimers. We also synthesized a pair of the C1″-epimers **4a**/**4b** without trying to control the stereochemistry of C-1″ because the stereochemistry of C-1″ remains to be determined. Therefore, as shown in the retrosynthetic analysis (Scheme 1), the mother spiroketals **4a** and **4b** could be regarded as the open-chain intermediate **5**, which would be further disconnected into two pieces **6** and **7**. Thus, we could see that both **6** and **7** contain the "1-oxygen-3-methyl" structure, which indicates that we could employ the naturally

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(1) Faulker and co-workers reported in a preliminary paper that **A** and **B** showed intense HIV activity, but in a later report they stated they would be artifacts formed from **C** as a result of prolonged storage in methanol or by autoxidations; see: (a) Potts, B. C. M.; Faulker, D. J. *J. Am. Chem. Soc.* **1991**, *113*, 6321. (b) Pika, J.; Faulkner, D. J. *Nat. Prod. Lett.* **1995**, *7*, 291.

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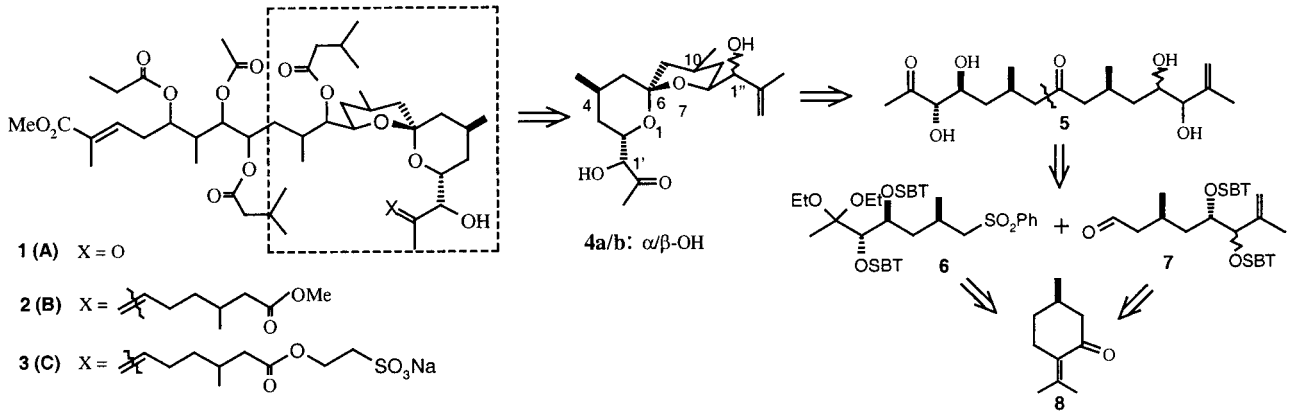
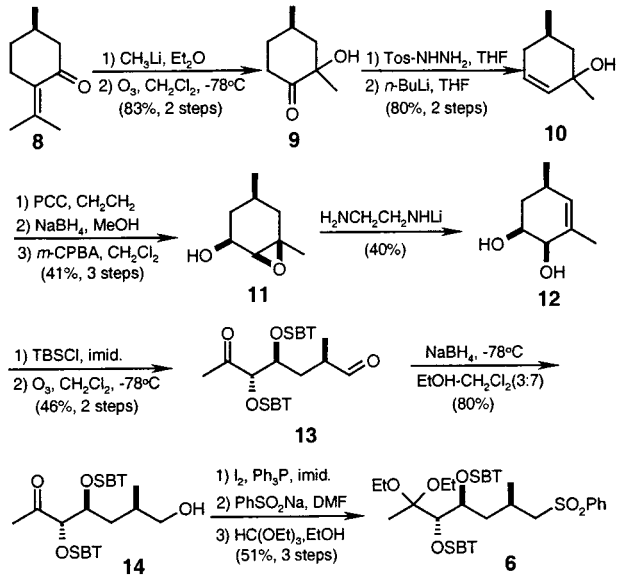
Scheme 1



abundant and easily available (*R*)-(+)-pulegone **8** containing a key chiral *R*-methyl group as the starting substrate.

The preparation of the intermediate **6** is presented in Scheme 2. Methylation of the carbonyl of pulegone **8** with

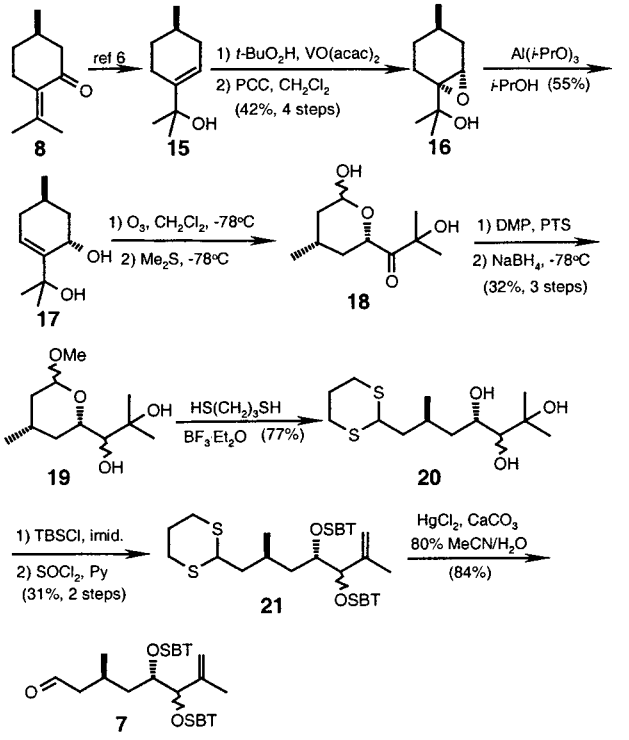
Scheme 2



MeLi and then ozonization−cleavage of the C=C bond afford the α-hydroxy ketone **9**, which is converted to the allylic alcohol **10** by hydrazonization with *p*-toluene hydrazine followed by treatment with the base *n*-BuLi.[2] The PCC oxidative rearrangement of the tertiary allylic alcohol **10**[3] followed by reduction of the formed ketone with $NaBH_4$ and then epoxidation with *m*-CPBA afford the α-hydroxy epoxide **11** as a single product, which undergoes a base-mediated rearrangement to give the allylic alcohol **12**.[4] We were not able to isolate the other diastereoisomers, so we have succeeded in diastereoselective construction of two chiral carbon centers bearing hydroxy groups. After protection of the hydroxy groups of **12** followed by ozonization−cleavage of the C=C bond, the open-chain ketone−aldehyde **13** was obtained. This aldehyde **13** was converted to a sulfone through three steps,[5] which is followed by the protection of the ketone carbonyl to give the intermediate **6**.

The preparation of second intermediate **7** is depicted in Scheme 3. Epoxidation of the tertiary α-hydroxy olefin **15**

Scheme 3



(prepared from pulegone[6]) with *t*-BuO_2H forms a mixture of **16** and its *syn*-epoxide isomer (75/25), which are hard to resolve on chromatography. Yet we have not been able to obtain the single epoxide **16** even by Sharpless asymmetric

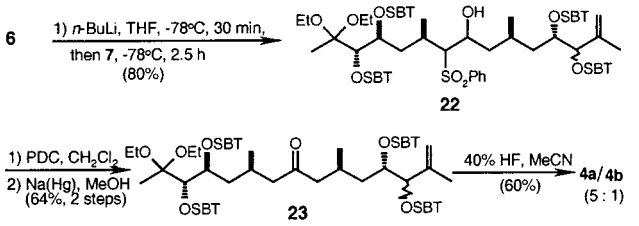
(2) Shapiro, R. H.; Heath, M. J. *J. Am. Chem. Soc.* **1967**, *89*, 5734−5735.

(3) Danben, W. G.; Michno, D. M. *J. Org. Chem.* **1977**, *42*, 682−685.

epoxidation. Fortunately, however, we succeeded in the purification of **16** by a PCC oxidation method we developed.[7] The successive Lewis acid-mediated rearrangement of **16** affords the allylic alcohol **17**, whose stereochemistry has been determined by 1D and 2D NMR.[8] Thus, we have succeeded in the diastereoselective construction of the hydroxy-bearing carbon center. The low yield of the allylic alcohol comes from the formation of a reductive rearrangement product.[8] The successive ozonization−cleavage of the C═C bond of **17** gives the open chain keto-aldehyde, which actually exists in the semiacetal **18** in two isomers (1/1). Protection of the hydroxy group of **18** with DMP followed by reduction of ketone carbonyl with $NaBH_4$ in situ gives a mixture of **19** as four isomers (5/5/1/1). We have not made any attempt to carry out the stereocontrolled reduction of the carbonyl for the reasons mentioned above. The major reduction product would be of the β-hydroxy configuration on the basis of either the transition-state analysis or the final configuration examination of 2D NMR spectroscopy of the acetonides of **20**.[9] Finally, the transacetalization of **19** with 1,3-thiopropanol, followed by the protection of two hydroxy groups with TBSCl and then dehydroxylation of the tertiary hydroxy, gives the compound **21** with the terminal double bond for the later functionalization, which is deacetalized to yield the intermediate **7** as a mixture of two isomers (5/1).

The coupling of **6** and **7** is carried out as showed in Scheme 4. Deprotonation of the sulfone **6** with *n*-BuLi and then quenching with aldehyde **7** yield the α-hydroxy sulfone

Scheme 4



22.[5c] Oxidation of the hydroxy group of **22** with PDC and then removal of the sulfone with 6% sodium amalgam gives the compound **23** as a mixture of two isomers (5/1) corresponding to the open-chain polyhydroxy intermediate **5**.[10] The successive full deprotection of the carbonyl and the hydroxy groups with hydrofluoric acid lead to both the deprotection and the auto-spirocyclization to form the final spiroketals as an oily mixture of only two C1″-epimers (5/1).[11] The isolated samples of **4a** and **4b** (10 mg and 2 mg) have been obtained by HPLC for structure determination by 1D and 2D NMR and mass spectroscopy.[12] Thus, we have succeeded in the stereocontrolled synthesis of the key mother spiroketals of the HIV-1 protease inhibitive didemnaketals. Further total synthetic studies and bioactive investigations are ongoing.

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(4) The literature reported the rearrangement of simple epoxide; here, we also had success with α-hydroxy epoxide, and the low yield possibly came from the influence of hydroxy the hydroxy substituent; see: (a) Gignere, R. J.; Hoffmann, M. R. *Tetrahedron Lett*. **1981**, *22*, 5039−5042. (b) Reggl, L.; Friedman, S.; Wender, I. *J. Org. Chem*. **1958**, *23*, 1136.

(5) (a) Ward, D. E.; Rhee, C. K. *Synth. Commun*. **1988**, *18*, 1927−1933. (b) Corey, E. J.; Pyne, S. G.; Su, W. *Tetrahedron Lett*. **1983**, *24*, 4883. (c) Morimoto, Y.; Mikami, A.; Kuwabe, S.; Shirahama, H. *Tetrahedron: Asymmertry* **1996**, *7*, 3371−3390.

(6) (a) Neidigk, D. D.; Morrison, H. *J. Chem. Soc., Chem. Commun*. **1978**, 601−602. (b) Neichinasi, E. H. *J. Org. Chem*. **1970**, *35*, 2010−2012.

(7) We have found that the mixture of **10** and its *syn*-epoxide isomer, when treated with 1.2 equiv of PCC (pyridine chlorochromate) in dry CH_2Cl_2 for ∼2 h at room temperature, yields the complex products and the unchanged **10**, which is readily isolable.

(8) Tu, Y. Q.; Sun, L. D.; Wang, P. Z. *J. Org. Chem.* **1999**, *64*, 629−633.

(9) The NOESY spectra for the major isomer of the acetonides of **20** show the strong correlations between H-5 and H-6 and between both H-5 and H-6 and the same acetonide methyl.

(10) Trost, B. M.; Arndt, H. C.; Strege, P. E.; Verhoeren, T. R. *Tetrahedron Lett*. **1976**, *17*, 3477.

(11) Collington, E. W.; Finch, H.; Smith, I. J. *Tetrahedron Lett*. **1985**, *26*, 681−684.

(12) **4a**/**b.** Spectral data of **4a**: ^{1}H NMR δ 5.01 (s, 1H), 4.96 (s, 1H), 4.17 (d, 1H, J = 5.2 Hz), 3.91 (ddd, 1H, J = 11.5, 5.4, 2.7 Hz), 3.86 (d, 1H, J = 6.0 Hz), 3.56 (ddd, 1H, J = 11.7, 6.0, 2.2 Hz), 2.59−0.88 (m, 10H), 2.31 (s, 3H), 1.75 (s, 3H), 1.15 (d, 3H, J = 7.3 Hz), 0.87 (d, 3H, J = 6.6 Hz); ^{13}C NMR δ 209.1, 143.9, 113.4, 98.7, 79.3, 78.3, 71.1, 67.3, 44.0, 40.1, 35.3, 31.5, 27.9, 24.8, 24.4, 22.0, 20.9, 18.2. Spectral data of **4b**: ^{1}H NMR δ 5.05 (s, 1H), 4.94 (s, 1H), 4.14 (brs, 1H), 4.09 (d, 1H, J =3.9 Hz), 3.88 (ddd, 1H, J =11.6, 5.7, 2.8 Hz), 3.60 (ddd, 1H, J = 12.0, 4.0, 2.4 Hz), 2.31−0.88 (m, 10H), 2.32 (s, 3H), 1.73 (s, 3H), 1.18 (d, 3H, J = 7.3 Hz), 0.88 (d, 3H, J = 6.5 Hz); ^{13}C NMR δ 209.5, 143.3, 112.1, 98.8, 79.2, 76.8, 71.3, 67.6, 44.0, 40.1, 31.9, 29.7, 28.2, 24.7, 24.6, 22.1, 20.6, 19.3.