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Tuning efficiency of the 4-*exo-trig* cyclization by the electronic effect: ring closure of 3,3-difluoro-4-pentenyl carbon radicals and synthesis of a *gem*-difluorocyclobutane nucleoside†

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4-*exo-trig* Cyclization reaction of a 4-pentenyl carbon radical containing the *gem*-difluoromethylene moiety adjacent to a radical accepting α,β-unsaturated ester was found to proceed efficiently to furnish a novel *gem*-difluorocyclobutane derivative. The cyclized product could be transformed into a *gem*-difluoromethylene analogue of oxetanocin T.

Oxetanocin A (**1**)[1] is a nucleoside antibiotic isolated from *Bacillus megaterium* (Fig. 1). Due to the unique four-membered oxetanose moiety conferring promising anti-viral properties,[2] considerable efforts have been devoted to the synthesis of **1**, and its base- or sugar-modified derivatives.[3] Interestingly, the thymine analogue of oxetanocin T **2**[4] also exhibits anti-HIV activity. As a sugar-modified derivative, cyclobutane nucleoside **3**[5] has been synthesized and reported to possess promising anti-HBV activity. In this context, we have envisaged that a novel nucleoside **4**, in which the oxetanose ring oxygen of **2** is replaced with a geminal-difluoromethylidene (CF_2) group, would show promising antiviral activities, as the CF_2 group has been suggested as an isopolar and isosteric substituent for oxygen.[6]

Intramolecular cyclization of carbon-centered radicals to unsaturated bonds has been widely used for the construction of cyclopentanes or cyclohexanes *via* 5-*exo*, 6-*exo* or 6-*endo-trig* mode according to Baldwin's rule.[7,8] In contrast, there have been only a few examples of 4-*exo-trig* cyclization reactions of 4-pentenyl carbon radicals leading to cyclobutane rings.[9] Successful ring closures have relied upon the *gem*-dialkyl effect.[9,10] During the course of our synthetic studies of **4** by radical cyclization, we found that the electron-withdrawing effect of the fluorine atom facilitates the 4-*exo-trig* cyclization. In this communication we report these results and their application to the synthesis of **4**.

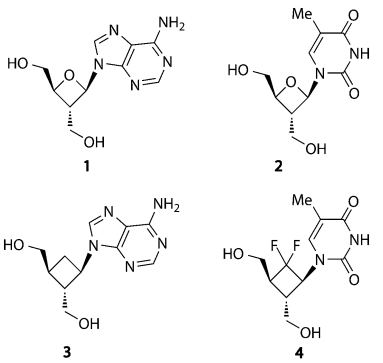

Fig. 1 Structure of compounds **1–4**.

There are three possible 4-pentenyl carbon radicals shown as **A–C** leading to the *gem*-difluorocyclobutane structure *via* 4-*exo-trig* cyclization reaction (Fig. 2). Initially, **5a**, which is a precursor of the 1,1-difluoro-4-pentenyl carbon radical **A**, was reacted with Bu_3SnH in the presence of AIBN in refluxing toluene. This reaction gave target **6a** in 29% yield (*cis*/*trans* = 3/1). However, a major product was the reduced product **7a** (32%). 2,2-Difluoro-carbon-radical **B** generated from **5b** failed to cyclize and gave a complex mixture.

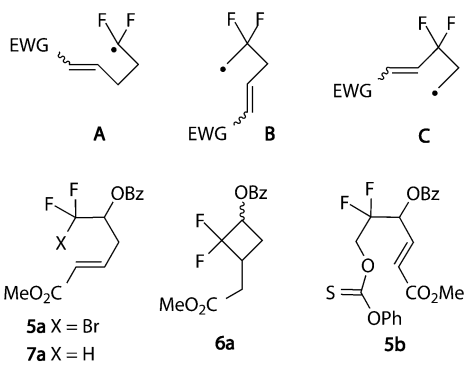

Fig. 2 Plausible radical intermediates **A–C** and their model compounds.

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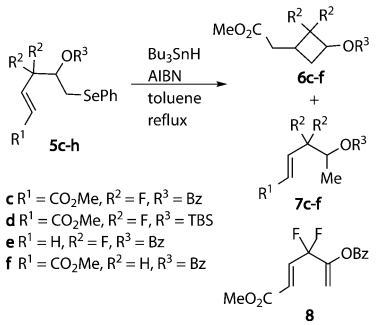
Table 1 Radical reaction of **5c–5f**[a]

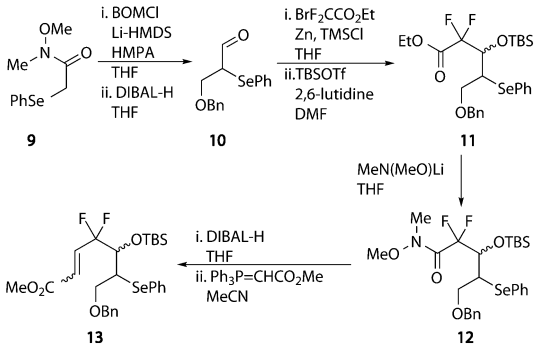


Entry	Precursor	Yield [%] of **6** (ratio; *cis*/*trans*)	Yield [%] of **7**
1	**5c**	72 (2/1)	12[b]
2	**5d**	91 (2/1)[c]	—
3	**5e**	—	72
4	**5f**	22[d]	61

[a] Reaction was carried out in refluxing toluene using 2.0 equiv. of Bu_3SnH and 0.2 equiv. of AIBN (dropwise addition over 4 h). [b] Compound **8** was obtained in 7% yield. [c] The ratio was calculated by the integration of ^{1}HNMR. [d] The stereochemistries of **6f** were not determined.

In contrast to these results, when **5c** was subjected to the same reaction conditions for the ring-closure of **5a**, intramolecular 4-*exo*-*trig* cyclization of the resulting 3,3-difluoro-4-pentenyl carbon radical **C** efficiently proceeded to give the target difluorocyclobutane **6a** in 72% yield (*cis*/*trans* = 2 : 1), along with the reduction product **7c** (12%) and diene **8** (7%) (Table 1, entry 1). As shown in entry 2, TBS-protected **5d** gave **6d** (*cis*/*trans* = 2 : 1) in 91% isolated yield. As can be seen in entry 3, the simple alkene **5e** lacking the electron-withdrawing group gave reduced product **7e** as a sole product in 72% yield (entry 3). A similar result was obtained in the case of the de-fluorinated analogue **5f** (entry 4). These results suggested that the efficiency of the 4-*exo*-*trig* cyclization was dependent upon the electron density of the double bond although the influence of the conformational change of each radical intermediate cannot be ruled out. To validate our assumption, SOMO and LUMO levels of the model intermediates were calculated based on Natural Bind Orbital (NBO) theory Table S1, see ESI.† As anticipated, the energy level of LUMO of **5c′** having both two fluorine atoms and unsaturated ester is lower than those of **5e′** and **5f′** lacking ester or two fluorine atoms. By taking the nucleophilic character of the carbon centered radical into consideration,[11] it would be reasonable that increasing electrophilicity of the radical-accepting unsaturated bond by fluorine substituents and ester facilitated the 4-*exo*-*trig* cyclization.

After optimization of the substrate for the radical cyclization, we have turned our attention to the synthesis of the difluoromethylene analogue **4** of oxetanocin T **2**. For the synthesis of the target molecule, we needed to prepare the radical precursor **13** and the synthetic route is illustrated in Scheme 1. Initially, Weinreb amide **9**[12] was treated with Li-HMDS and subsequently BOMCl in one pot to give the α-benzyloxymethylated product, which was then reduced by DIBAL-H to furnish the aldehyde **10** in 47% yield. Compound **10** was subjected to Reformatsky reaction utilizing BrF_2CCO_2Et and activated zinc[13] followed by silylation of the resulting secondary alcohol to give **11** in 77% yield.



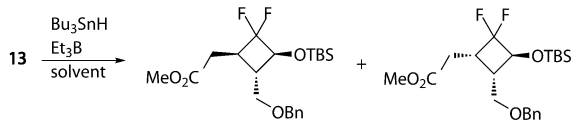
Scheme 1 Preparation of radical precursor **13**.

The ester **11** was then converted into the Weinreb amide **12** in excellent yield (90% yield). DIBAL-H reduction of **12** and subsequent Wittig reaction gave the desired substrate **13** [a mixture of three stereoisomers; *ca.* major-(*E*)-**13** : minor-(*E*)-**13** : (*Z*)-**13** = 1 : 0.22 : 0.14].

With the substrate **13** in hand, we next carried out the radical cyclization and the results are summarized in Table 2. As shown in entry 1, when **13** was reacted with Bu_3SnH under the conditions described in Table 1, the yield of the desired difluorocyclobutane derivative **14** was unexpectedly decreased to 38% yield (diastereomeric mixture: *ca.* 2 : 1). On the basis of NOE experiments, the major isomer was found to be *trans*,-*trans*-**14** with the minor isomer being *trans*,*cis*-**14**, respectively (see ESI†). To improve the yield of **14**, the reaction was carried out at ambient temperature using Et_3B as an initiator under an O_2 atmosphere. As can be seen in entries 2 to 5, the longer the duration time of the dropwise addition of Bu_3SnH, the better the isolated yield of **14** although the ratio of *trans*,*trans*-**14**/*trans*,*cis*-**14** was unchanged.[14] The best result was obtained when Bu_3SnH was added dropwise over 24 h to give **14** in 78% yield (entry 5). No improvement was observed at −20 °C due to the recovery of **13** (47%) (entry 6).

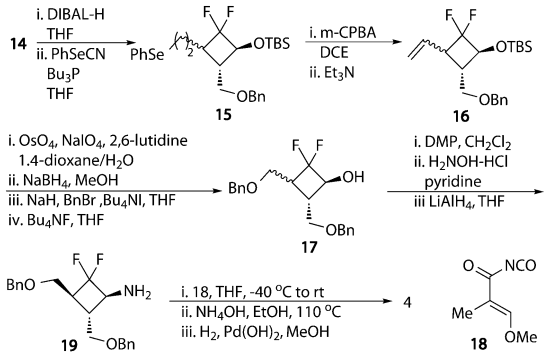
Finally, conversion of **14** to the target **4** was performed (Scheme 2). DIBAL-H reduction of an epimeric mixture of **14** and subsequent phenylselenylation of the resulting hydroxyethyl derivative by using PhSeCN and Bu_3P[15] gave **15** in 97% yield in two steps. The selenide **15** was converted to terminal olefin **16**

Table 2 Radical cyclization of **13**



Entry	Solvent	Temp (°C)	Time[a] (h)	Yield [%] of **14**	Ratio[b] (*trans*,*trans*/*trans*,*cis*)
1	Toluene	110[c]	4	38	2.0/1
2	Benzene	rt	2	72	2.7/1
3	Benzene	rt	4	70	2.7/1
4	Benzene	rt	8	77	2.6/1
5	Benzene	rt	24	78	2.6/1
6	Toluene	−20	48	48[d]	3.0/1

[a] Bu_3SnH was dropwise added at an indicated time. [b] The ratio (*trans*,*trans*/*trans*,*cis*) was calculated by integration of ^{1}HNMR. [c] AIBN was used as an initiator. [d] Compound **13** was recovered in 47%.



Scheme 2 Synthesis of **4**.

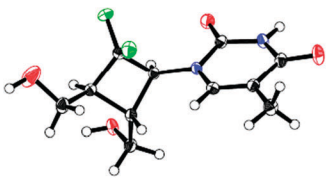


Fig. 3 ORTEP drawing of compound **4**.

(86% yield) by oxidation with *m*-CPBA and subsequent *syn*-elimination of the respective selenoxide. Next, **16** was transformed into **17** (diastereomeric mixture; *ca.* 3 : 1) in 65% yield through the following four steps: (1) Lemieux–Johnson oxidation in the presence of 2,6-lutidine,[16] (2) $NaBH_4$ reduction of the resulting aldehyde, (3) benzylation of the primary alcohol, (4) removal of the TBS group by using Bu_4NF. Next, the cyclobutylamine **19** was synthesized through (1) Dess–Martin periodinane (DMP) oxidation of **17**, (2) oximation of the ketone, (3) $LiAlH_4$ reduction of the oxime.[17] Although, the yield was not satisfied (32%), amine **19** was obtained as a single stereoisomer. Finally, **19** was transformed into the corresponding thymine nucleoside by a reported procedure[18] using isocyanate **18**. Debenzylation with $Pd(OH)_2/C$ gave the title compound **4** in 56% yield. The relative stereochemistry of **4** was assigned by NOE experiments (see ESI†) and confirmed by X-ray crystallographic analysis (Fig. 3).

It was found that the 4-*exo*-*trig* cyclization reaction of the 3,3-difluoro-4-pentenyl carbon radical efficiently proceeded to furnish the novel *gem*-difluorocyclobutane. The electron withdrawing effect of the two fluorine atoms adjacent to the radical accepting double bond accelerated the cyclization reaction. As a synthetic application of this radical ring closure, the synthesis of difluoromethylene oxetanocin T **4**, a potential anti-viral agent, was achieved. Anti-viral assay revealed that compound **4** did not show any activity against HIV-1, VZV and HCMV.

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