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Stereoselective Route to Oxetanocin Carbocyclic Analogues Based on a [2 + 2] Photocycloaddition to a Chiral 2(5*H*)-Furanone

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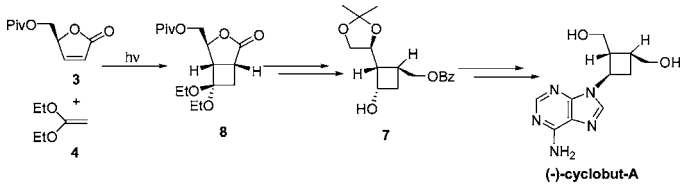
ABSTRACT



The synthesis of the trisubstituted cyclobutane 7, which is a suitable precursor for the preparation of oxetanocin carbocyclic analogues, is described. The key step involves a regio- and diastereoselective [2 + 2] photochemical reaction of ketene diethyl acetal with (*S*)-5-pivaloyloxymethyl-2(5*H*)-furanone, 3. As an application of this methodology, (–)-cyclobut-A has been prepared from the intermediate 7.

Oxetanocin-A, **1a**, is a naturally occurring oxetane adenine nucleoside (Figure 1), which was isolated from the fermentation broth of *Bacillus megaterium*[1] in 1986. This compound was found to exhibit a broad spectrum of antiviral activity, including herpes simplex virus 1 and 2 (HSV-1, HSV-2), varicella zoster virus (VZV), human cytomegalovirus (HCMV), and human immunodeficiency virus (HIV).[2] More recently, its synthetic analogues oxetanocin-G,[3] **1b**, and oxetanocin-T,[4] **1c**, have also been described as potent antiviral agents.

oxetanocin-A, **1a** (B: adenine)
oxetanocin-G, **1b** (B: guanine)
oxetanocin-T, **1c** (B: thymine)

cyclobut-A, **2a** (B: adenine)
cyclobut-G, **2b** (B: guanine)

Figure 1. Oxetanocins and carbocyclic analogues.

The unique structure of oxetanocin-A coupled with its biological activity prompted organic chemists to explore the potential of four-membered carbocyclic nucleosides. Thus, in 1989, the syntheses of the oxetanocin analogues cyclobut-A, **2a**, and cyclobut-G, **2b**, were described.[5,6] It was found that these compounds were active against a broad spectrum of herpes viruses and HIV.[7] Since then, the carbocyclic analogues of oxetanocin-A have received considerable at-

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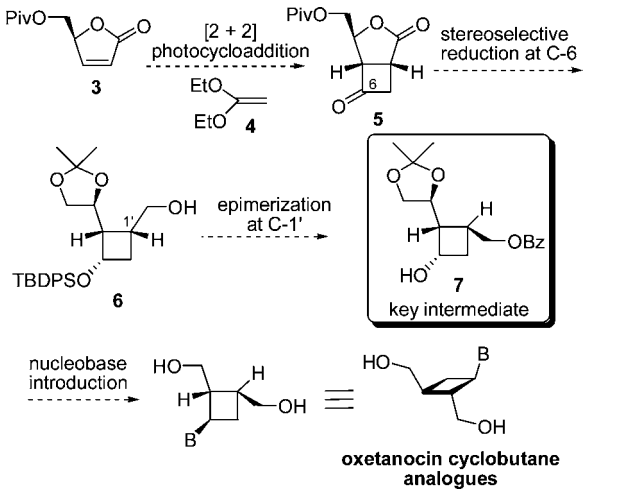
tention that has culminated in different total syntheses.[8] Because opposite enantiomers can display different pharmacological and toxicological properties,[9] the synthesis of enantiomerically pure compounds is required. Nevertheless, among the reported investigations, only a few synthetic approaches were devised to provide optically active carbocyclic oxetanocins (A and G), including optical resolution[10] and stereoselective synthesis.[11] Most of these approaches involve a large number of steps or they present moderate enantioselectivity, resulting in relatively low overall yields. Consequently, a further refined synthetic approach to enantiomerically pure oxetanocin carbocyclic analogues is still awaited.

As part of our efforts to synthesize novel cyclobutane nucleosides and evaluate them as antiviral agents, herein we describe a practical route to a suitably trisubstituted cyclobutane, **7**, which can be used as a key common intermediate for the preparation of oxetanocin carbocyclic analogues. As an application of this methodology, (−)-cyclobut-A has been prepared.

(*S*)-5-Pivaloyloxymethyl-2(5*H*)-furanone, **3**, was visualized as an appropriate starting material to undertake the synthesis of the target cyclobutane nucleosides through the strategy depicted in Scheme 1. Our plan involved four main transformations: (i) cyclobutanone construction by a regio- and diastereoselective [2 + 2] photocycloaddition of **3** to 1,1-diethoxyethylene, **4**, followed by removal of the acetal group; (ii) stereoselective reduction of the ketone; (iii) epimerization at C-1′; and (iv) nucleobase introduction onto the cyclobutane moiety of **7**.

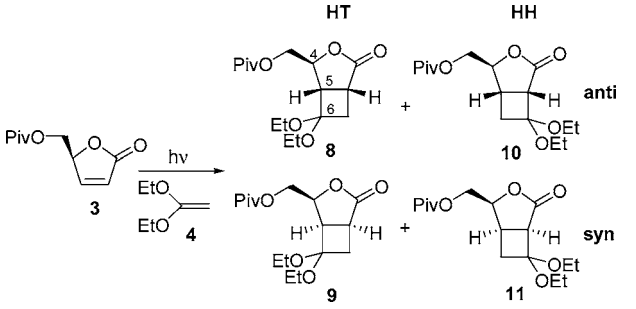
Accordingly, our initial efforts focused on the preparation of the key cyclobutanone unit **5**. The photochemical reaction of 5-substituted 2(5*H*)-furanones to ketene dialkyl acetals has received little attention,[12] and to the best of our knowledge, a diastereoselective version has not yet been

Scheme 1. Synthetic Strategy to Oxetanocin Cyclobutane Analogues



investigated. This photochemical reaction could lead to the formation of up to four compounds, the head-to-head (HH) and head-to-tail (HT) anti isomers and the HH and HT syn isomers (Table 1). It has been reported that the photocycloaddition of cyclic enones to electron-rich alkenes occurs with predictable regioselectivity, giving mainly HT adducts,[13] although slight variations of the reaction conditions, particularly the solvent, can dramatically change the regioselectivity.[14] Hence, we have examined the effect of the

Table 1. Photochemical Reaction of Lactone **3** to 1,1-Diethoxyethylene, **4**



solvent[a]	yield[b] (%)	**8/9/10/11**[c]	HT/HH	anti/syn
acetonitrile	61	50:22:21:7	72:28	71:29
ether	75	58:34:5:3	92:8	63:37
hexane	72	52:39:6:3	91:9	58:42

[a] Irradiation through a quartz filter at −20 °C. [b] Isolated yield of the mixture of stereoisomers after column chromatography. [c] Isomer ratio from GC analysis of the reaction crude.

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solvent on the regio- and diastereoselectivity of the photocycloaddition of **4** to furanone **3**, which has previously shown good facial selectivity in its photochemical reactions with ethylene, acetylene, vinylene carbonate, and 1,2-dichloroethylene.[15]

Irradiation of a solution of lactone **3** (7.7 mM) and a 10-fold excess of olefin **4** in acetonitrile with a high-pressure mercury lamp through a quartz filter for 2 h at −20 °C afforded the photoadducts **8**−**11** in 61% global yield and a ratio 50:22:21:7 (Table 1). Since chromatographic separation of these adducts was rather cumbersome, NMR analyses of enriched samples had to be performed. The anti/syn configuration of the cycloadducts was determined by the value of the coupling constant between H-4 and H-5[15] (∼2 Hz for the anti isomers **8** and **10** and ∼ 6 Hz for the syn isomers **9** and **11**), while the connectivity was established by HMBC experiments, wherein a correlation between the acetal carbon atom C-6 and proton H-4 is observed for the HT adducts **8** and **9**.

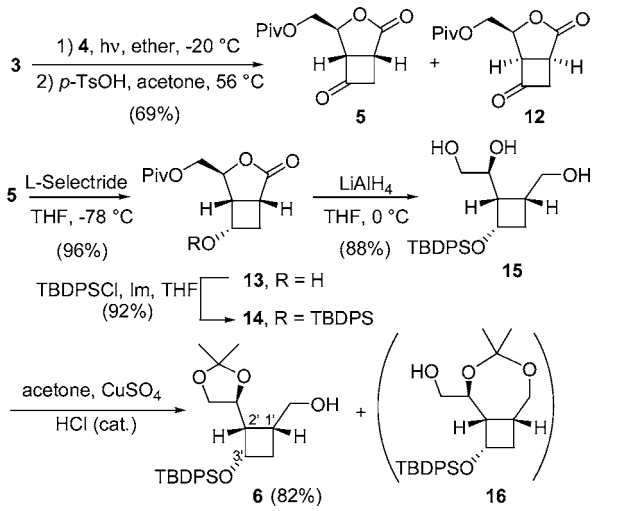
An important solvent effect was noticed when the reaction was performed in less polar solvents. In ether, after 2.5 h of irradiation through a quartz filter, both the yield (75%) and regioselectivity (HT/HH = 92:8) were remarkably increased, whereas the stereoselectivity decreased slightly (anti/syn = 63:37). Similar results were found in hexane. When the reaction was carried out in acetone through a Pyrex filter, only low yields of the expected cycloadducts were obtained because the formation of an oxetane by addition of ketene acetal **4** to acetone competed advantageously.[12b]

For synthetic purposes, the photocycloaddition was performed in ether and the reaction crude was treated with *p*-TsOH in acetone without previous purification. This protocol afforded a 2:1 mixture of the HT-anti and HT-syn cyclobutanones, **5** and **12**, easily separable by column chromatography, from which the major isomer **5** could be isolated in 46% yield for the two steps (Scheme 2).

The stereoselective reduction of ketone **5** from the less hindered face of the cyclobutane, performed by reaction with L-Selectride in THF at −78 °C, delivered alcohol **13** in excellent yield. Subsequent silylation of the hydroxyl group, followed by $LiAlH_4$ reduction, provided triol **15** in 80% yield for the two steps. Protection of the vicinal diol as the isopropylidene acetal **6** was achieved in 82% yield by reaction of **15** with acetone in the presence of anhydrous copper sulfate and catalytic HCl.[16] Other reaction conditions such as treatment with 2,2-dimethoxypropane and catalytic camphorsulfonic acid in acetone, or acetone/catalytic HCl, furnished variable amounts of the seven-ring acetonide **16**.

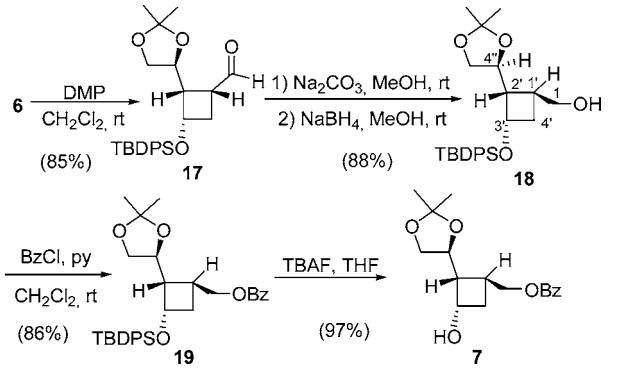
The next key transformation involved reversing the configuration at C-1′ in **6**. In view of the steric congestion existent at the neighboring carbon atom, it was expected that

Scheme 2



the corresponding aldehyde would epimerize easily.[17] Dess−Martin periodinane (DMP) oxidation of **6** furnished the aldehyde **17** in 85% yield (Scheme 3), but the initial attempts

Scheme 3



to epimerize it using Et_3N,[18] DBU in CH_2Cl_2,[19] DMAP in THF, or *p*-TsOH in CH_2Cl_2 met with failure, leading only to recovery of the starting material or poor proportions of the desired epimer. It was eventually found that treatment of **17** with Na_2CO_3 in MeOH[20] provided the trans aldehyde, which was reduced immediately with $NaBH_4$ to the corresponding alcohol. The epimer **18** was isolated in 88% yield for the two steps, along with a minor amount of **6** (7% yield). The inversion of configuration at C-1′ of **18** was established by a NOESY experiment, where cross-peaks between H-1′ and protons H-4″ and H-4′endo and between H-3′ and protons H-2′ and H-4′exo were observed.

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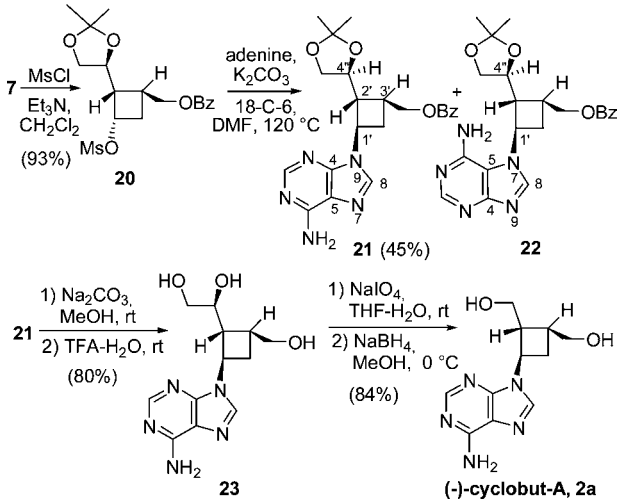
Benzoylation of the primary alcohol of **18** under standard conditions followed by selective removal of the silyl protecting group with TBAF provided the key intermediate **7** in 84% yield for the two steps.

Once a practical route to **7** had been established, we turned our attention to the preparation of (−)-cyclobut-A. The displacement of a mesylate group by adenine was considered as a plausible methodology to couple the purine base to the cyclobutane moiety. Accordingly, cyclobutanol **7** was treated with MsCl and Et_3N in CH_2Cl_2 to afford mesylate **20** in 93% yield (Scheme 4), which reacted with adenine in the presence

Scheme 4



of K_2CO_3 and 18-crown-6 ether, in DMF at 120 °C for 7 h, furnishing the expected *N*-9-coupled product **21** in 45% yield, along with traces of the *N*-7 regioisomer **22**. Extensive NMR spectral data, including HMBC and NOESY experiments, provided strong support for the structures of compounds **21** and **22**. The assignment of the attachment site of the purine base on **21** was established by an HMBC experiment, which showed correlation between H-1′ and the carbon atoms C-4 and C-8. Its relative stereochemistry was determined by the NOESY spectrum that shows cross-peaks between H-1′ and H-4″. For compound **22**, NOE correlations observed between the amine group (NH_2) and H-1′ as well as the dioxolane methyne proton H-4″, and also between H-8 and H-1′, are consistent with a *N*-7 coupled nucleoside. The regiochemistry of each product was also supported by the higher field chemical shift value of adenine C-4 carbon of the *N*-9 isomer **21** (δ 150.2) compared to that of the *N*-7 isomer **22** (δ 160.6), due to the larger steric congestion existing in the former.[21]

Removal of the protecting groups of **21** was accomplished by sequential treatment with Na_2CO_3 in methanol and trifluoroacetic acid−H_2O giving **23** in 80% overall yield. Oxidative cleavage of the vicinal diol of **23** with $NaIO_4$, followed by reduction of the intermediate aldehyde with $NaBH_4$, provided the target (−)-cyclobut-A as a crystalline solid in 84% overall yield. Its NMR spectra and physical properties matched with those previously reported in the literature, $[\alpha]_D$ −14.3 (*c* 0.7, H_2O) [lit.[10b] $[\alpha]_D$ −13.5 (*c* 1.0, H_2O)].

The synthetic intermediate **23** is a cyclobut-A nucleoside analogue bearing an additional hydroxymethyl group. Hence, we decided to screen it for antiviral activity. As a preliminary test, it has been evaluated for anti-HIV activity. This compound was found to be inactive against HIV-1 NL4-3 strain in MT-4 cells at concentrations up to 25 μg/mL.

In summary, we have reported a practical synthesis of the trisubstituted cyclobutane **7**, which is a versatile precursor for the preparation of oxetanocin carbocyclic analogues. From this intermediate, we have completed the synthesis of (-)-cyclobut-A, **2a**, in six steps and 28% overall yield.

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Supporting Information Available: Experimental details, characterization data, ^1H and ^{13}C NMR spectra of all new compounds, and anti-HIV activity of compound **23**. This material is available free of charge via the Internet at http://pubs.acs.org.

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