Efficient Total Synthesis of Racemic and Optically Active Cyclobut-A and Simple Analogues†

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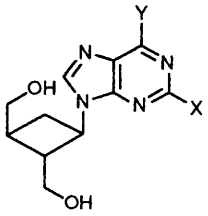
Rapid synthesis of the potent antiviral agent, cyclobut-A, **1a**, from the inexpensive starting materials maleic anhydride and acetylene, in both racemic and optically active forms, is described; the route also allows for the preparation of several hydroxylated and keto analogues in good overall yield.

In 1989 Honjo and coworkers[1] prepared the unnatural products, cyclobut-A and cyclobut-G, **1a**, **b**, carbocyclic analogues of the known antiviral agent oxetanocin A,[2] and demonstrated that they were strongly antiviral.[1] Since then these compounds have been prepared by a number of different routes[3] and have been shown to exhibit very high activity against HIV infections.[4] We report here a new, very efficient synthesis which affords cyclobut-A **1a** in 20% overall yield from the inexpensive, readily available anhydride **3** and permits the preparation of novel analogues of cyclobut-A, namely the alcohols **11** and **13** and the ketone **14**.

Photocycloaddition of acetylene to maleic anhydride **2** has been carried out by several groups and proceeds in good yield (69–72%) to give the anhydride **3** (Scheme 1).[5] Treatment of **3** with sodium methoxide in methanol effected both methanolysis and epimerization to afford a mixture of the *trans* and *cis* monoesters **4** in which the *trans* isomer greatly predominated (~5 : 1).‡ This mixture was not purified but rather directly



1a; X = H, Y = NH_2
1b; X = NH_2, Y = OH

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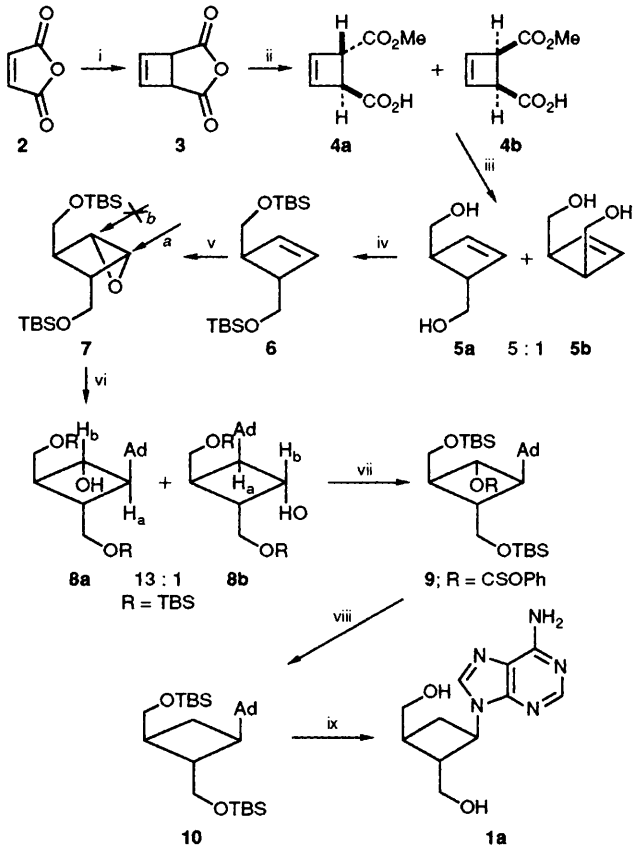
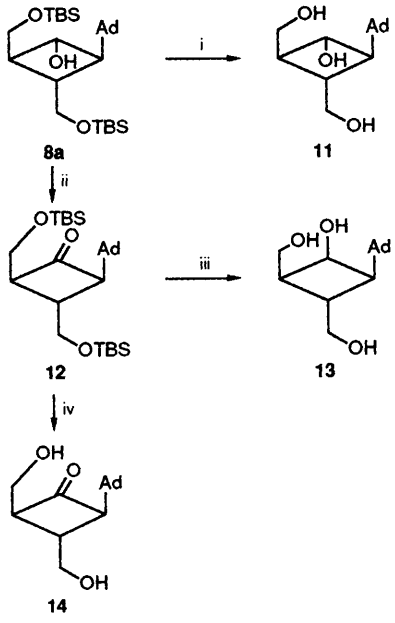
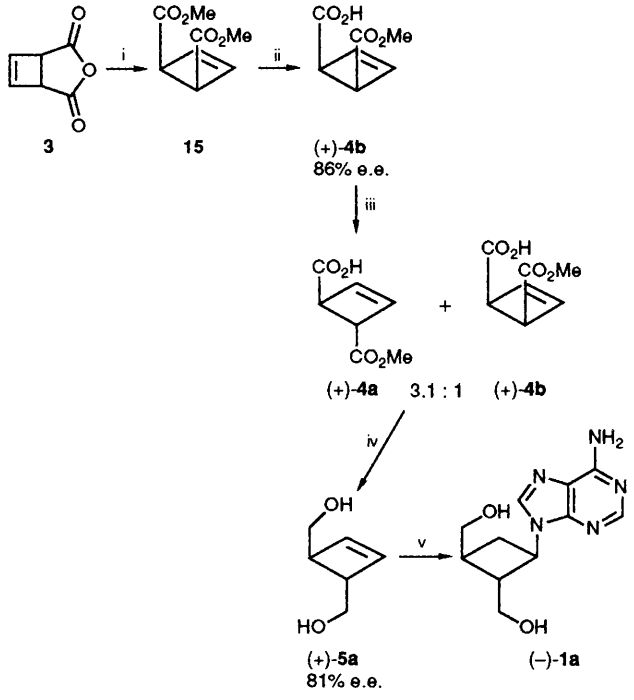
‡ The stereochemistry of the *cis* and *trans* dimethyl 3-cyclobutene-1,2-dicarboxylates was easily assigned by heating them to ~100 °C for 2 h and analysing the known *E*,*E*- and *E*,*Z*-isomers of dimethylhexa-2,4-dienoates (~5.5 : 1) by ^{1}H NMR.



Scheme 1 *Reagents and conditions*: i, HC≡CH, acetone, *hν*, 69–72%; ii, NaOMe–MeOH; iii, $LiAlH_4$, 62% **5a** from **3**; iv, *tert*-butyldimethylsilyl chloride (TBSCl), 1*H*-imidazole, dimethylformamide, 99%; v, *m*-chloroperbenzoic acid, CH_2Cl_2, 98%; vi, NaH, AdH, DMSO, 18-crown-6, 114 °C, 28 h, 59%; vii, PhOCSCl, 4-dimethylaminopyridine, MeCN, 18 h, 83%; viii, Bu^n_3SnH, azoisobutyronitrile, heat, dioxane, 30 min, 73%; ix, AcOH–H_2O (4 : 1), 90 °C, 1.5 h, quant.



Scheme 2 *Reagents and conditions*: i, AcOH–H_2O (4 : 1), 90 °C, 1.5 h, 96%; ii, PCC–CH_2Cl_2, 75%; iii, (*a*) L-Selectride, tetrahydrofuran (THF), 95% (*b*) AcOH–H_2O, 91%; iv, AcOH–H_2O, 94%



Scheme 3 *Reagents and conditions*: i, MeOH, H_2SO_4, 25 °C, 48 h, 94%; ii, immobilized PLE, acetone, pH 7 buffer, 92%, iii, LDA (2 equiv.), THF, −78 °C; H_3O^+, 95%; iv, $LiAlH_4$; SiO_2, 53% **5a** from **4b**; v, as before

reduced to an easily separable 5 : 1 mixture of the *trans* and *cis* diols **5a,b**, from which the desired *trans* isomer **5a** could be isolated in 62% yield for the two steps from **3**.[6] Protection of this C_2-symmetric diol as the bis-(*tert*-butyldimethylsilyl)ether **6** and epoxidation furnished the epoxide **7** in nearly quantitative yield for the two steps (only one epoxide is possible due to the C_2 symmetry of the bis-ether). Opening of the epoxide was accomplished with high regioselectivity by treating **7** with adenine (AdH) and sodium hydride in dimethyl sulfoxide (DMSO) in the presence of 18-crown-6 at 114 °C for 28 h. This produced a 13 : 1 mixture of the all-*trans* isomer **8a** and a minor byproduct, tentatively assigned the *trans-cis-trans* structure **8b**,§ in 59% yield (Ad = 7-adenyl). Compound **8a** can be isolated free of its isomer by crystallization from dichloromethane–hexane (52% yield from **7**). Not surprisingly, opening of the epoxide *via* path *a* is greatly favoured over that *via* path *b* due to the much larger steric hindrance associated with the latter mode of attack. The stereochemistry of **8a** was tentatively assigned on the basis of the expected favoured approach of attack and the pattern of the coupling constants of the methine protons in the high field ^1H NMR spectrum of **8a** (H_a: δ 4.19, dd, *J* 7.7, 7.2 Hz; H_b: δ 4.10, dd, *J* 8.1, 6.9 Hz).[7] This tentative assignment was confirmed when **8a** was converted into cyclobut-A **1a** as follows. Deoxygenation of the secondary alcohol of **8a** was carried out by a Barton radical process,[8] namely formation of the *O*-phenyl thiocarbonate **9** (83%) and reduction with tri(n-butyl)stannane (73%) to give the bis-silyl ether of cyclobut-A **10** in 61% overall yield for the two-step operation. Final acid-catalysed desilylation furnished the desired antiviral agent, cyclobut-A **1a**, in quantitative yield, thus ending an efficient eight-step synthesis which proceeds in 20% overall yield from **3**. The synthetic material was identical to an authentic sample by ^1H and ^{13}C NMR.

This synthetic approach allowed us to prepare several analogues of cyclobut-A unavailable by other routes. For example, hydrolysis of the silyl ethers of **8a** afforded in 96% yield the triol **11**, a hydroxylated analogue of cyclobut-A (Scheme 2). The epimeric triol **13** could also be easily prepared. Oxidation of **8a** with pyridinium chlorochromate (PCC) in dichloromethane produced in 75% yield the ketone **12** which was then reduced from the less hindered face with L-Selectride to give the *trans-cis-cis* isomer of **8a**. Acidic hydrolysis furnished the desired triol **13**, another hydroxylated analogue of **1a**. Finally removal of the silyl protecting groups from the ketone **12** afforded compound **14**, the keto analogue of cyclobut-A.

We have also completed a simple chiral synthesis of (−)-cyclobut-A (−)-**1a** based on similar chemistry (Scheme 3). Opening of the anhydride **3** with acidic methanol afforded the known *cis*-diester **15** in high yield.[9] This diester contains a plane of symmetry and therefore should be a good candidate for enzymatic enantioselective hydrolysis. Treatment of **15** with pig liver esterase (PLE) at pH 7 gave the desired monoester which was somewhat difficult to separate from the enzyme.[10] However the use of PLE immobilized on a modified azlactone mixed polymer¶ in a pH 7 buffer containing 5% acetone afforded the desired optically active monoester (+)-**4b** in 92% chemical yield with an enantiomeric excess (e.e.) of 86% [determined by ^1H NMR measurements of the diastereoisomeric (*S*)-α-methylbenzylamine salts]. All that remained was to isomerize the correct carbonyl group, which was accomplished by treatment with 2 equiv. of lithium diisopropylamide (LDA) to generate the dianion followed by quenching at −78 °C to give a 3.1 : 1 mixture of the desired *trans* monoester (+)-**4a** and the starting material (+)-**4b**. Direct reduction of the mixture followed by chromatography produced the desired (*S,S*)-diol (+)-**5a** in an overall yield of 53% from (+)-**4b**. The e.e. of this diol was determined to be 81% by examination of the ^1H NMR spectra of the bis-Mosher's esters of both (+)-**5a** and the racemic compound **5a**. The synthesis of optically active (−)-cyclobut-A, (−)-**1a**, was

§ The small amount of this material, and the fact that it could not be obtained pure, did not permit a definite assignment of its structure. Although we favour structure **8b**, we cannot rule out other reasonable alternatives, *e.g.* the corresponding 9-adenyl isomer of **8a**.

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carried out exactly as described for the racemic series in comparable yields.‖

We are currently extending this efficient synthesis to the preparation of other similar cyclobutyl nucleosides, *e.g.* cyclobut-G **1b**, and further analogues in both the racemic and optically active series. The analogues **11**, **13** and **14** are currently being tested for antiviral activity (both CMV and HIV), the results of which will be reported when they are available.

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‖ The $[\alpha]_D^{25}$ for our synthetic (−)-**1a** was −11.57 (*c* 1.0 in water), which compares to the value of −13.5 given by Slusarchyk *e al.* in ref. 3.