

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

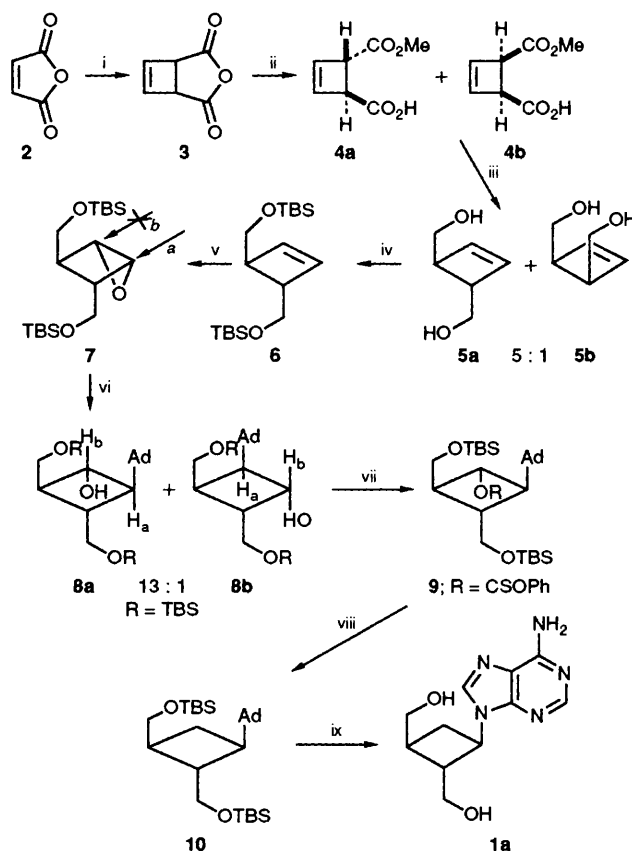
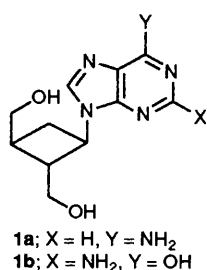
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Rapid synthesis of the potent antiviral agent, cyclobut-A, **1a**, from the inexpensive starting materials maleic anhydride and acetylene, in both racemic and optically active forms, is described; the route also allows for the preparation of several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

In 1989 Honjo and coworkers<sup>1</sup> prepared the unnatural products, cyclobut-A and cyclobut-G, **1a**, **b**, carbocyclic analogues of the known antiviral agent oxetanocin A,<sup>2</sup> and demonstrated that they were strongly antiviral.<sup>1</sup> Since then these compounds have been prepared by a number of different routes<sup>3</sup> and have been shown to exhibit very high activity against HIV infections.<sup>4</sup> 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**.

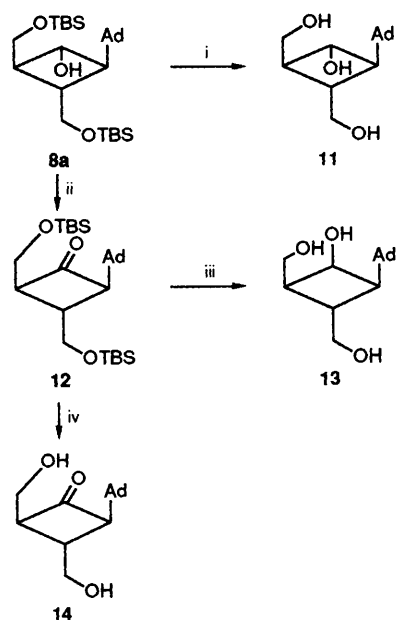
Photocycloaddition of acetylene to maleic anhydride **2** has been carried out by several groups and proceeds in good yield (69–72%) to give the anhydride **3** (Scheme 1).<sup>5</sup> Treatment of **3** with sodium methoxide in methanol effected both methanolysis and epimerization to afford a mixture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



**Scheme 1** Reagents and conditions: i, HC≡CH, acetone, *hν*, 69–72%; ii, NaOMe–MeOH; iii, LiAlH<sub>4</sub>, 62% **5a** from **3**; iv, *tert*-butyldimethylsilyl chloride (TBSCl), 1*H*-imidazole, dimethylformamide, 99%; v, *m*-chloroperbenzoic acid, CH<sub>2</sub>Cl<sub>2</sub>, 98%; vi, NaH, AdH, DMSO, 18-crown-6, 114 °C, 28 h, 59%; vii, PhOCsCl, 4-dimethylaminopyridine, MeCN, 18 h, 83%; viii, Bu<sub>3</sub>SnH, azoisobutyronitrile, heat, dioxane, 30 min, 73%; ix, AcOH–H<sub>2</sub>O (4:1), 90 °C, 1.5 h, quant.

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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 <sup>1</sup>H NMR.

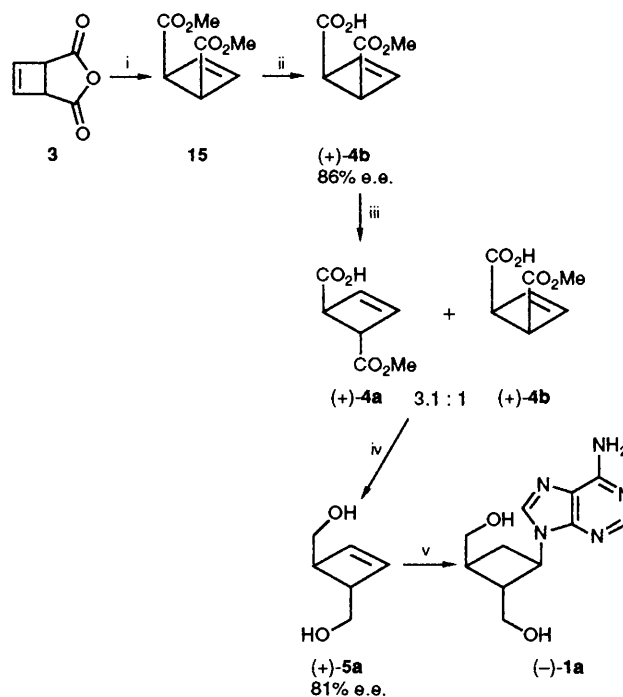


**Scheme 2** Reagents and conditions: i, AcOH-H<sub>2</sub>O (4:1), 90 °C, 1.5 h, 96%; ii, PCC-CH<sub>2</sub>Cl<sub>2</sub>, 75%; iii, (a) L-Selectride, tetrahydrofuran (THF), 95% (b) AcOH-H<sub>2</sub>O, 91%; iv, AcOH-H<sub>2</sub>O, 94%

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**.<sup>6</sup> Protection of this C<sub>2</sub>-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<sub>2</sub> 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**,<sup>§</sup> 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 <sup>1</sup>H NMR spectrum of **8a** (H<sub>a</sub>: δ 4.19, dd, *J* 7.7, 7.2 Hz; H<sub>b</sub>: δ 4.10, dd, *J* 8.1, 6.9 Hz).<sup>7</sup> 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,<sup>8</sup> 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 <sup>1</sup>H and <sup>13</sup>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%

§ 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**.



**Scheme 3** Reagents and conditions: i, MeOH, H<sub>2</sub>SO<sub>4</sub>, 25 °C, 48 h, 94%; ii, immobilized PLE, acetone, pH 7 buffer, 92%, iii, LDA (2 equiv.), THF, -78 °C; H<sub>3</sub>O<sup>+</sup>, 95%; iv, LiAlH<sub>4</sub>; SiO<sub>2</sub>, 53% **5a** from **4b**; v, as before

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.<sup>9</sup> 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.<sup>10</sup> However the use of PLE immobilized on a modified azlactone mixed polymer<sup>¶</sup> 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 <sup>1</sup>H NMR measurements of the diastereoisomeric (*S,S*)- $\alpha$ -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 <sup>1</sup>H 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

¶ Generously supplied by Dr Steve Heilman, 3M, St Paul, MN.

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 *et al.* in ref. 3.