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A method for the stereospecific conversion of 1,3-diols into oxetanes

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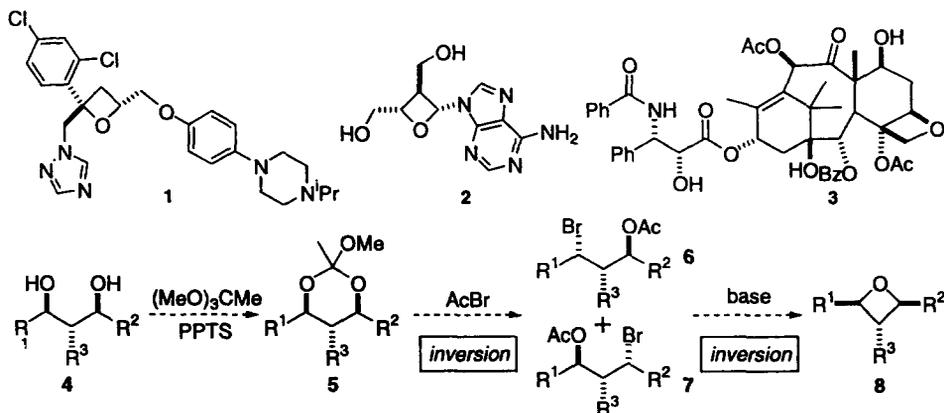
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Abstract

Diastereomerically pure 1,3-diols were converted into the corresponding orthoesters and reacted with acetyl bromide to give bromoacetates with inversion of configuration at a benzylic position. Methanolysis and cyclisation gave diastereomerically pure 2,4-disubstituted oxetanes. © 1999 Elsevier Science Ltd. All rights reserved.

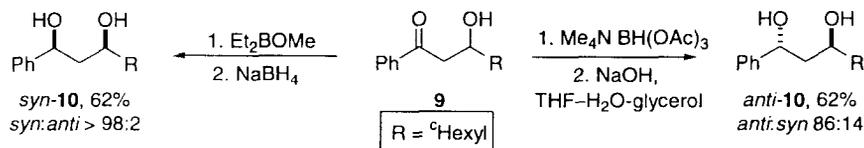
The four-membered oxetane ring is found in a number of biologically active compounds including the antifungal triazole¹ **1**, the antiviral nucleoside² **2** and the anticancer agent³ Taxol **3**. Oxetanes are usually synthesised by photochemical [2+2] cycloaddition⁴ of aldehydes and alkenes; although often highly stereoselective, this reaction usually restricted the synthesis of one of the possible diastereomeric products. Another approach involves the activation of one of the alcohols of a 1,3-diol (e.g. **4**), followed by ring-closure,⁵ but the ratio of oxetanes obtained generally depends on the regioselectivity of the activation reaction.



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In this paper, we describe the development of a method for oxetane synthesis which allows genuine *choice* over the stereochemistry of the products. Conversion of 1,3-diols (which are readily synthesised as single diastereomers^{6,7}) into the corresponding orthoesters (e.g. **5**), and treatment with acetyl bromide, was expected to give the regioisomeric acetoxy bromides (such as **6** and **7**), which should close to give the same oxetane (e.g. **8**). The key to the strategy lies in the two inversion reactions (**5**→**6** or **7**; **6** or **7**→**8**) which should ensure that the stereochemistry of all three stereogenic centres of **4** is retained in the product **8**. This strategy has been previously applied to the synthesis of optically active epoxides⁸ and diamines.⁹

The aldol **9** was prepared in >98% yield by reacting the lithium enolate of acetophenone with cyclohexanecarboxaldehyde. *Syn*- and *anti*-selective reduction⁷ of the aldol **9** gave the diastereomeric diols *syn*- and *anti*-**10** (Scheme 1).^{10,11} Reaction conditions were screened to optimise the yield and stereospecificity of the conversion of the diols *syn*- and *anti*-**10** into the acetoxybromides **11** and **12** (Table 1).^{12,13} Treatment of the diols *syn*- and *anti*-**10** with 45% HBr in acetic acid¹⁴ gave the same 25:75 mixture of the acetoxy bromides **11** and **12** indicating that the transformation was not stereospecific under these conditions (entries 1 and 2). A higher level of stereospecificity was observed using acetyl bromide (entries 3 and 4); here, participation (**14** arrows) must be faster than acylation of the intermediate hydroxyacetate. However, the best result was observed when the diols **10** were converted into the orthoesters **15**, cooled to -78°C and treated with acetyl bromide (entries 5 and 6); under these conditions, the reaction was stereospecific: the diols *syn*- and *anti*-**10** were converted into **11** and **12**, respectively.



Scheme 1.

The acetoxybromides **11** and **12** were converted into the corresponding hydroxybromides **17** and **19** by reduction with ¹Bu₂AlH (Scheme 2). We screened a range of reaction conditions for the cyclisation of the hydroxybromide **17** to the oxetane **18**, which was obtained in 26% yield by refluxing with sodium hydride in THF.^{15,16} The by-products of the cyclisation **17**→**18** were those obtained from the fragmentation **16**. The yield of **20** was higher than that of **18**, presumably because cyclisation was less unfavourable with the substituents on opposite faces of the forming ring (Fig. 1).

Table 1
 Synthesis of the acetoxy bromides **11** and **12**

Entry	Starting material	Conditions	Yield ^a	
			11+12	11 : 12
1	<i>syn</i> - 10	HBr, AcOH, 25 °C	96%	25:75
2	<i>anti</i> - 10 ^c	HBr, AcOH, 25 °C	96%	25:75
3	<i>syn</i> - 10	AcBr, CH ₂ Cl ₂ , $-78 \rightarrow 25^{\circ}\text{C}$	>98%	91:9
4	<i>anti</i> - 10 ^d	AcBr, CH ₂ Cl ₂ , $-78 \rightarrow 25^{\circ}\text{C}$	>98%	48:52
5	<i>syn</i> - 10	1. (MeO) ₃ CMe, PPTS, CH ₂ Cl ₂ , 25 °C; 2. AcBr, $-78 \rightarrow 25^{\circ}\text{C}$	>98%	>98:2
6	<i>anti</i> - 10 ^d	1. (MeO) ₃ CMe, PPTS, CH ₂ Cl ₂ , 25 °C; 2. AcBr, $-78 \rightarrow 25^{\circ}\text{C}$	>98%	15:85
7	<i>syn</i> - 10	1. (MeO) ₃ CMe, PPTS, CH ₂ Cl ₂ , 25 °C; 2. AcBr, 25 °C	>98	84:16
8	<i>syn</i> - 10	1. (MeO) ₃ CH, PPTS, CH ₂ Cl ₂ , 25 °C; 2. AcBr, $-78 \rightarrow 25^{\circ}\text{C}$	<i>e</i>	>90:10

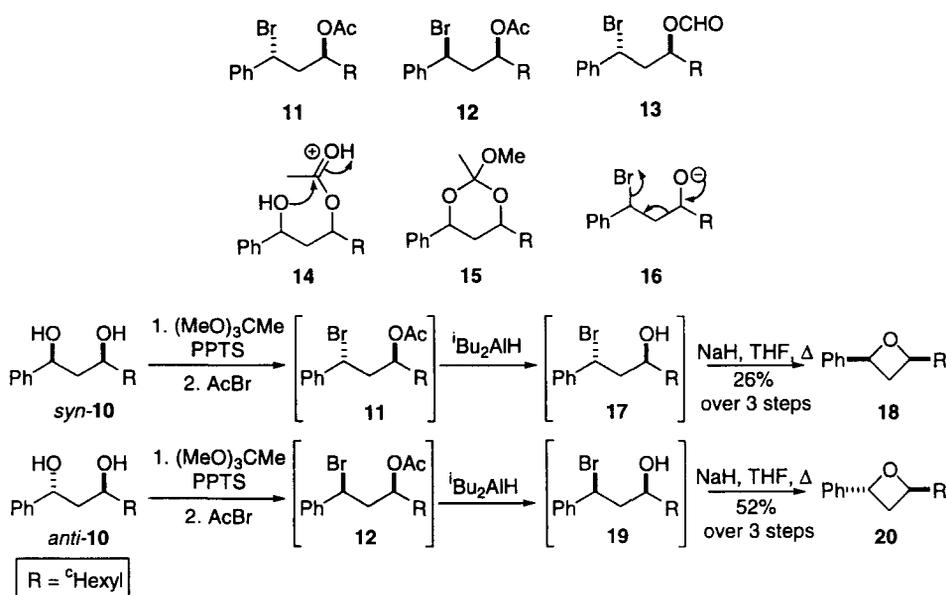
^aYield of mixture of **11** and **12**.

^bMeasured by 300 MHz ¹H NMR.

^c68:32 mixture of *anti*- and *syn*-**10**.

^d86:14 mixture of *anti*- and *syn*-**10**.

^eCompound **13** observed by 300 MHz ¹H NMR; yield of **13** not measured.



Scheme 2.

We have also developed a convenient two-pot procedure for the conversion of 1,3-diols into the corresponding oxetanes (Scheme 3).¹⁷ The crude acetoxybromides **11** and **12**, synthesised as before, were treated with sodium hydride (3 equiv.) and methanol (1 equiv.) in refluxing THF; deprotection and cyclisation gave the corresponding oxetanes. The conversion of the diol¹⁰ **22** into the corresponding oxetane proved a particularly stern test of stereospecificity. The product of the reaction was not the expected oxetane *cis,cis*-**23** (but its diastereoisomer *trans,cis*-**23**) presumably because formation of the benzylic cation was competitive with the usual S_N2 pathway. Other cyclisations suffer loss of stereospecificity in particularly unfavourable cases.¹⁸

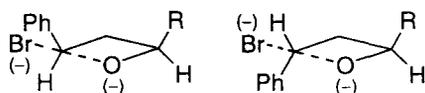
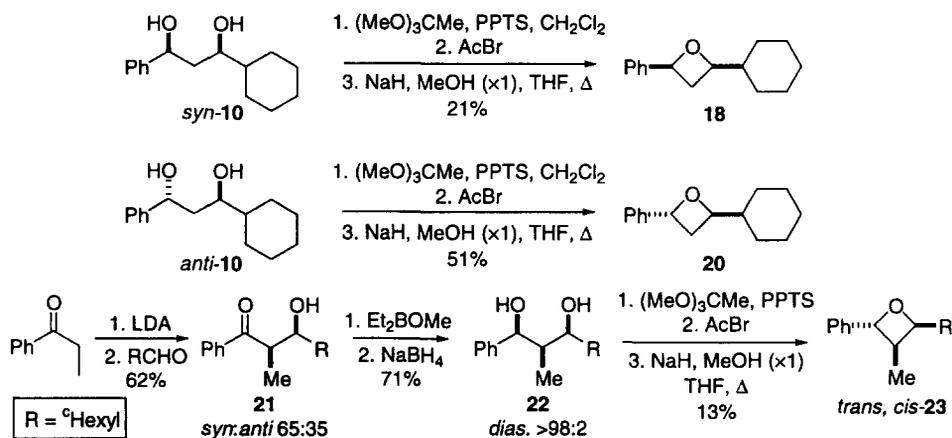


Figure 1.



Scheme 3.

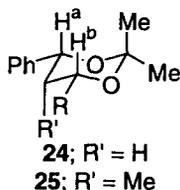
In summary, we have developed a convenient method for the conversion of 1,3-diols into the corresponding oxetanes. The reaction is generally stereospecific but the stereospecificity is lost when cyclisation is particularly unfavourable.

Acknowledgements

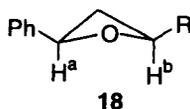
We thank the Nuffield Foundation for undergraduate bursaries (to T.A. and J.H.) and Pfizer and the AstraZeneca Strategic Research Fund for additional support. We are grateful to Dr. Martin Christlieb for preliminary work and Dr. Stuart Warriner for useful discussions.

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10. The stereochemistry of the diol *syn*-**10** and **22** was proved by conversion into the corresponding acetonides **24** and **25**. The ^{13}C chemical shifts of the acetonides,¹¹ the coupling constants around the six-membered rings and the observation of a mutual NOE enhancement between H^a and H^b proved the relative stereochemistry in each case.



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12. The regiochemistry of the acetoxybromides **11** and **12** was proved using an HMBC experiment: a crosspeak was observed between the carbonyl carbon and *CHOAc*.
13. The acetoxybromides **11** and **12** and the hydroxybromides **17** and **19** epimerised on standing.
14. (a) Golding, B. T.; Hall, D. R.; Sakrikar, S. *J. Chem. Soc., Perkin Trans. I* **1973**, 1214; (b) Fleming, P. R.; Sharpless, K. B. *J. Org. Chem.* **1991**, *56*, 2869.
15. The coupling constants around the oxetanes were typical¹⁶ [$^3J_{\text{HH}}$: 8–9 Hz (*syn*), 6–7 Hz (*anti*)]. A mutual NOE was observed between H^a and H^b in the oxetane **18**.



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17. Experimental procedure: Trimethylorthoacetate (132 μl , 1.04 mmol) and pyridinium *p*-toluenesulfonate (2 mg) were added to a stirred solution of the diol *anti*-**10** (202 mg, 0.84 mmol) in dichloromethane (4 ml). The reaction mixture was stirred for 10 min at room temperature, cooled to -78°C and acetyl bromide (156 μl , 2.158 mmol) was added. The reaction

was stirred for 1.5 h, quenched with saturated sodium bicarbonate solution, extracted with dichloromethane (3×5 ml), dried (MgSO_4), filtered and evaporated to give a crude product. The crude product was dissolved in dry THF (5 ml) and methanol (39 μl , 0.95 mmol) and sodium hydride (104 mg, 60% dispersion in oil, 2.59 mmol) were added. The vessel was wrapped in foil and the reaction stirred for 24 h at 60°C, quenched with water and extracted with ethyl acetate (3×15 ml). The combined organic extracts were dried (MgSO_4), filtered, evaporated and purified by flash chromatography. Compound **18**: δ_{H} (500 MHz, CDCl_3) 7.43–7.25 (5H, m, Ph), 5.66 (1H, app t, $J=7.8$, PhCH), 4.47 (1H, app q, $J=7.9$), 2.88 (1H, dt, $J=10.8$ and 6.9), 2.31 (1H, dt, $J=10.8$ and 8.1), 2.01 (1H, m) and 1.8–0.8 (10H, m). Compound **20**: δ_{H} (500 MHz, CDCl_3) 7.43–7.25 (5H, m, Ph), 5.58 (1H, dd, $J=8.5$ and 6.2, PhCH), 4.49 (1H, app q, $J=6.2$), 2.75 (1H, ddd, $J=14.5$, 8.5 and 6.2), 2.56 (1H, ddd, $J=14.5$, 8.5 and 6.2), 2.02 (1H, m) and 1.9–0.8 (10H, m). Compound **23**: δ_{H} (500 MHz, CDCl_3) 7.43–7.26 (5H, m, Ph), 5.08 (1H, d, $J=6.0$, PhCH), 4.43 (1H, dd, $J=10.2$, 8.0, $\text{CH}^{\text{c}}\text{Hex}$), 2.92 (1H, app. sextet, $J=7.2$, CHMe), 2.07–0.71 (11H, m, $^{\text{c}}\text{Hex}$) and 1.30 (3H, d, $J=7.2$, Me).

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