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

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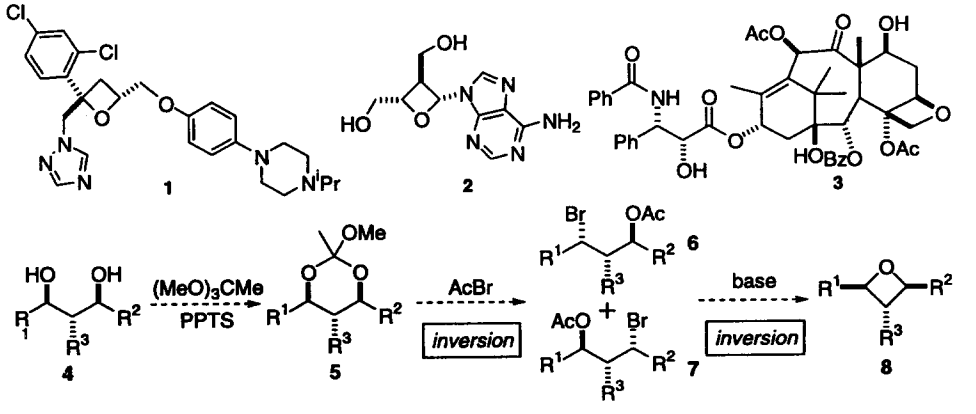
Abstract

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 triazole[1] **1**, the antiviral nucleoside[2] **2** and the anticancer agent[3] Taxol **3**. Oxetanes are usually synthesised by photochemical [2+2] cycloaddition[4] 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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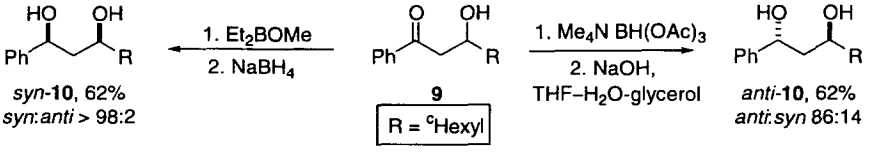
In this paper, we describe the development of a method for oxetane synthesis which allows genuine *choice* over the stereochemistry of the products. Conversion of 1,3-diols (which are readily synthesised as single diastereomers[6,7]) into the corresponding orthoesters (e.g. **5**), and treatment with 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 epoxides[8] and diamines.[9]

The aldol **9** was prepared in >98% yield by reacting the lithium enolate of acetophenone with cyclohexanecarboxaldehyde. *Syn*- and *anti*-selective reduction[7] 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 acid[14] 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.



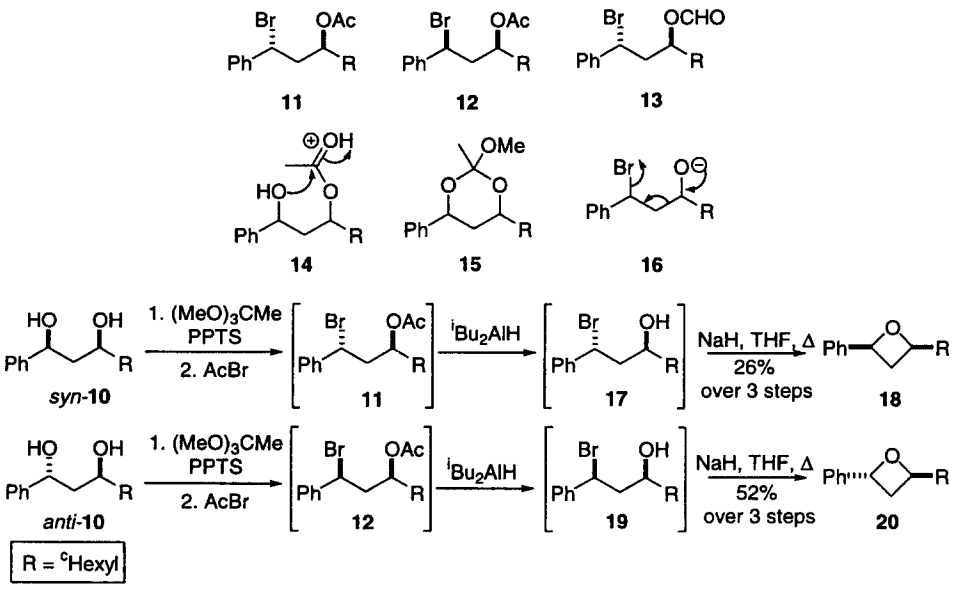
Scheme 1.

The acetoxybromides **11** and **12** were converted into the corresponding hydroxybromides **17** and **19** by reduction with $^{i}Bu_2AlH$ (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	Ratio[b] 11 : 12
1	*syn*-**10**	HBr, AcOH, 25 °C	96%	25:75
2	*anti*-**10**[c]	HBr, AcOH, 25 °C	96%	25:75
3	*syn*-**10**	AcBr, CH_2Cl_2, −78 → 25 °C	>98%	91:9
4	*anti*-**10**[d]	AcBr, CH_2Cl_2, −78 → 25 °C	>98%	48:52
5	*syn*-**10**	1. $(MeO)_3CMe$, PPTS, CH_2Cl_2, 25 °C; 2. AcBr, −78→25 °C	>98%	>98:2
6	*anti*-**10**[d]	1. $(MeO)_3CMe$, PPTS, CH_2Cl_2, 25 °C; 2. AcBr, −78→25 °C	>98%	15:85
7	*syn*-**10**	1. $(MeO)_3CMe$, PPTS, CH_2Cl_2, 25 °C; 2. AcBr, 25 °C	>98	84:16
8	*syn*-**10**	1. $(MeO)_3CH$, PPTS, CH_2Cl_2, 25 °C; 2. AcBr, −78→25 °C	*e*	>90:10

[a]Yield of mixture of **11** and **12**.
[b]Measured by 300 MHz ^1H NMR.
[c]68:32 mixture of *anti*- and *syn*-**10**.
[d]86:14 mixture of *anti*- and *syn*-**10**.
[e]Compound **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 diol[10] **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]

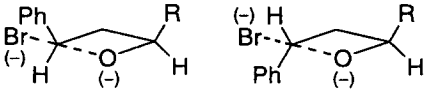
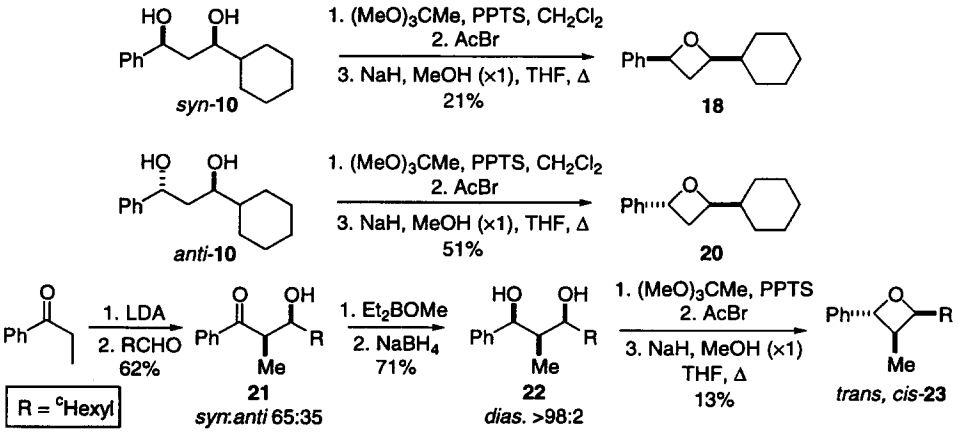


Figure 1.



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

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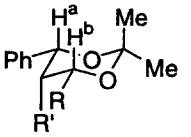
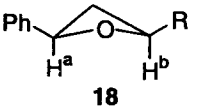
10. The stereochemistry of the diol *syn*-**10** and **22** was proved by conversion into the corresponding acetonides **24** and **25**. The ^{13}C chemical shifts of the acetonides,[11] the coupling constants around the six-membered rings and the observation of a mutual NOE enhancement between H^a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



24; R' = H
25; R' = Me

11. Evans, D. A.; Reiger, D. L.; Gage, J. R. *Tetrahedron Lett.* **1990**, *30*, 7099.
12. The regiochemistry of the acetoxybromides **11** and **12** was proved using an HMBC experiment: a crosspeak was observed between the carbonyl carbon and C*H*OAc.
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. 1* **1973**, 1214; (b) Fleming, P. R.; Sharpless, K. B. *J. Org. Chem.* **1991**, *56*, 2869.
15. The coupling constants around the oxetanes were typical[16] [$^3J_{HH}$: 8–9 Hz (*syn*), 6–7 Hz (*anti*)]. A mutual NOE was observed between H^a and H^b in the oxetane **18**.



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, PhC*H*), 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, PhC*H*), 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, PhC*H*), 4.43 (1H, dd, *J*=10.2, 8.0, C*H*^{c}Hex), 2.92 (1H, app. sextet, *J*=7.2, C*H*Me), 2.07–0.71 (11H, m, ^{c}Hex) and 1.30 (3H, d, *J*=7.2, Me).

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