ORGANIC LETTERS

2006
Vol. 8, No. 8
1629−1632

Stereoselective Synthesis of Protected 1,2-Diols and 1,2,3-Triols by a Tandem Hydroboration–Coupling Sequence

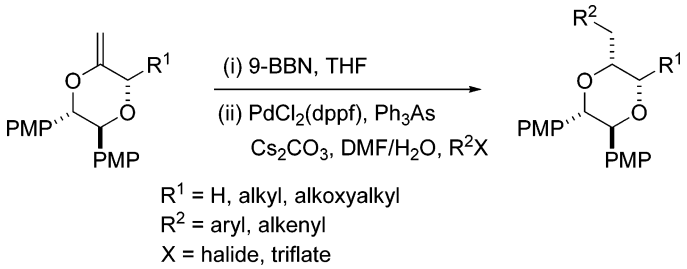
Manmohan Kapur, Anton Khartulyari, and Martin E. Maier*

Institut für Organische Chemie, Universität Tübingen, Auf der Morgenstelle 18, D-72076 Tübingen, Germany

martin.e.maier@uni-tuebingen.de

Received January 25, 2006

ABSTRACT



A new approach to complex chiral diols and polyols is described utilizing a tandem hydroboration/Suzuki cross-coupling reaction. This method utilizes the versatility of a glycolate-derived chiral template.

Clusters of two or more vicinal hydroxyl groups are frequently found in natural products. Examples include carbohydrates and some macrolides. Because of the importance of 1,2-diols and 1,2,3-triols, a range of methods have been developed for their synthesis. For example, carbon−carbon bond-forming reactions on suitable substrates can be used. Thus, aldol reactions,[1] addition reactions to α-hydroxy aldehydes,[2] Pinacol couplings,[3] or epoxide opening reactions[4] have been employed in this context. In addition, carbon−oxygen bond forming reactions such as epoxidation[5,6] or dihydroxylation[7] are valuable options. However, the famous Sharpless asymmetric dihydroxylation is less suitable for the synthesis of *anti*- and 1,2-diols. Finally, carbon−hydrogen bond forming reactions (reductions) on carbonyl-containing substrates can be considered. The choice of a certain strategy is largely governed by other groups in the near or somewhat remote vicinity of the diol.

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(3) For some recent examples, see: (a) Barden, M. C.; Schwartz, J. *J. Am. Chem. Soc.* **1996**, *118*, 5484−5485. (b) Lipski, T. A.; Hilfiker, M. A.; Nelson, S. G. *J. Org. Chem.* **1997**, *62*, 4566−4567. (c) Takai, K.; Morita, R.; Toratsu, C. *Angew. Chem.* **2001**, *113*, 1150−1153. (d) Yamamoto, Y.; Hattori, R.; Miwa, T.; Nakagai, Y.-i.; Kubota, T.; Yamomoto, C.; Okamoto, Y.; Itoh, K. *J. Org. Chem.* **2001**, *66*, 3865−3870. (e) Schmidt, R. R.; Frische, K. *Liebigs Ann. Chem.* **1988**, 209−214. (f) Takenaka, N.; Xia, G.; Yamamoto, H. *J. Am. Chem. Soc.* **2004**, 126, 13198−13199.

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10.1021/ol0602194 CCC: $33.50
Published on Web 03/14/2006

During our studies toward the synthesis of a complex benzolactone, an *anti*-diol flanked by a homoallylic double bond which itself is attached to a functionalized aryl ring was needed (Figure 1). Although homoallylic alcohols can

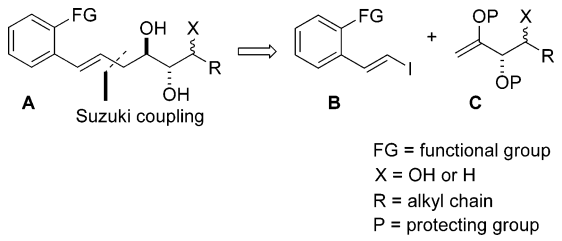


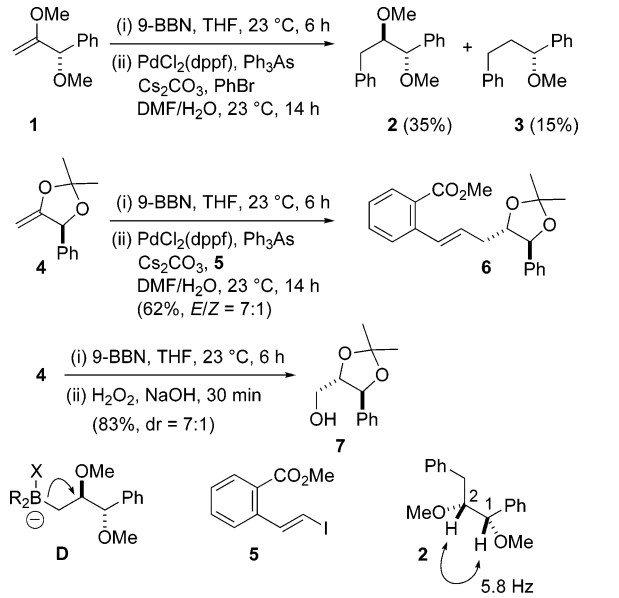
Figure 1. Hydroboration/cross-coupling strategy for the synthesis of complex diols.

be obtained by the addition of allylmetal compounds to aldehydes, this method is less attractive if a substituent is needed at the alkene terminus of the product (cf. structure **A**). To assemble a system of type **A**, we envisioned a tandem hydroboration/Suzuki coupling of α-alkoxy enol ethers **C** with vinyl halides such as **B**. In this paper, we show that exocyclic enol ethers prepared from 1,3-dioxolan-4-ones and 1,4-dioxan-2-ones are useful substrates for this strategy leading to complex diols in high diastereoselectivity.

Looking into the literature, there are only a few reports of hydroboration and Suzuki couplings of glycals derived from carbohydrates.[8] In most of these cases, *C*-glycosides were the target.[9] The hydroboration/oxidation of five-membered enol ethers has been reported by Sinaÿ.[10] An intramolecular diastereoselective hydroboration/Suzuki coupling tactic was employed by us in a synthesis of the macrolide salicylihalamide A.[11]

The present study was initiated with an acyclic system **1** derived in two easy steps from (*S*)-(+)-mandelic acid via esterification and Petasis methylenation.[12] Although it has been reported that these substrates are unreactive toward 9-BBN,[13] we found this not to be the case (Scheme 1). Given the tendency of *β*-alkoxy boranes to undergo syn-elimination (cf. intermediate **D**), the formation of some side products for the acyclic substrates was expected.[13] The result of the hydroboration followed by Suzuki cross-coupling with bromobenzene was a reasonable diastereoselectivity (90:10) but a moderate yield of 35% for the diol derivative **2**. The stereochemical outcome (anti) was confirmed by the coupling of 5.8 Hz for H-1/H-2. The spectral data for **2** were in complete agreement with the literature data.[14]

Scheme 1. Hydroboration Followed by Suzuki Coupling of Chiral Enol Ethers



In contrast, the investigations with the mandelic acid derived cyclic enol ether **4** afforded better results (Scheme 1). Thus, the hydroboration of **4** followed by Suzuki coupling with the vinyl iodide **5** afforded compound **6** in good yield as a mixture of double-bond isomers (*E*/*Z* = 7:1). The diastereomer resulting from the hydroboration step was not detected. Most likely, the trans-hydroboration intermediate reacts much faster in the cross-coupling reaction than the corresponding cis-diastereomer. The starting *E*-vinyl iodide **5** could be prepared in 74% yield by Takai olefination[15] of methyl 2-formylbenzoate. The *E*/*Z* ratio for the Takai reaction was found to be around 5:1 in this and other cases described below. Surprisingly, the stereochemical outcome (*syn*-diol) for the hydroboration of enol ether **4** was opposite to that reported by Sinaÿ.[10] An indication for this was the relatively high coupling constant for the vicinal protons in the dioxolane ring ($J = 8.6$ Hz) of compound **6**. To clarify this issue, hydroboration of the enol ether **4** was followed by oxidative workup which produced the known alcohol **7** (dr = 7:1).[16] This proved the diastereoselectivity of the hydroboration with 9-BBN. This result might be explained by a reversible hydroboration step. Attempts to couple the hydroboration product of **4** with *meta*-iodo-anisol led to

(8) Taillefumier, C.; Chapleur, Y. *Chem. Rev.* **2004**, *104*, 263−292.
(9) (a) Johnson, C. R.; Johns, B. A. *Synlett* **1997**, 1406−1408. (b) Johns, B. A.; Pan, Y. T.; Elbein, A. D.; Johnson, C. R. *J. Am. Chem. Soc.* **1997**, *119*, 4856−4865. (c) Kettle, J. G.; Clark, J. S. *Tetrahedron Lett.* **1997**, *38*, 123−126. (d) Sasaki, M.; Fuwa, H.; Inoue, M.; Tachibana, K. *Tetrahedron Lett.* **1998**, *39*, 9027−9030. (e) Sasaki, M.; Fuwa, H.; Ishikawa, M.; Tachibana, K. *Org. Lett.* **1999**, *1*, 1075−1077. (f) Campbell, A. D.; Paterson, D. E.; Raynham, T. M.; Taylor, R. J. K. *Chem. Commun.* **1999**, 1599−1600. (g) Takakura, H.; Noguchi, K.; Sasaki, M.; Tachibana, K. *Angew. Chem., Int. Ed.* **2001**, *40*, 1090−1093.
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(12) Petasis, N. A.; Bzowej, E. I. *J. Am. Chem. Soc.* **1990**, *112*, 6392−6394.
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(14) Tiecco, M.; Testaferri, L.; Tingoli, M.; Chianelli, D.; Bartoli, D. *Tetrahedron* **1988**, *44*, 2261−2272.
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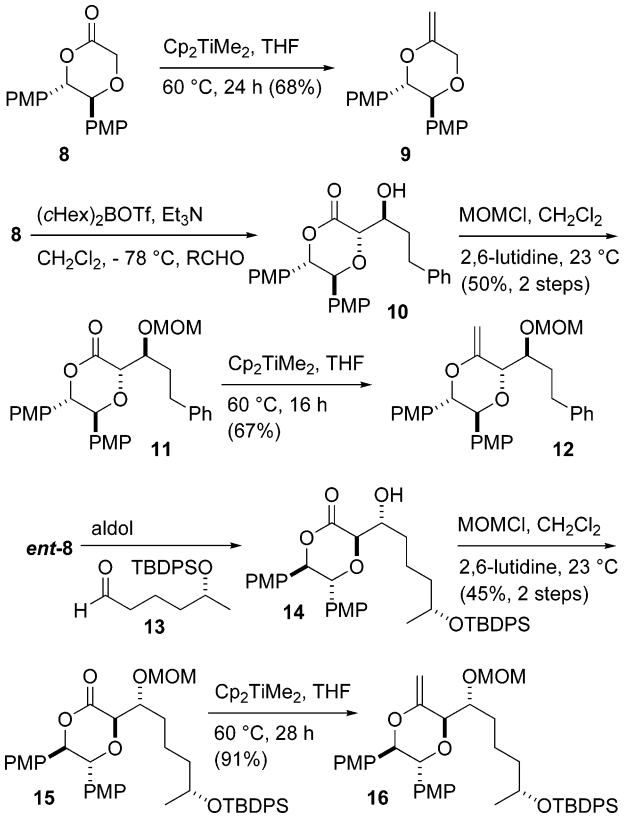
cleavage of the acetal.[17] Similar reactions using other five-membered *exo*-methylene compounds with aryl halides gave no results.

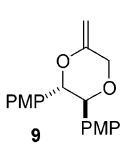
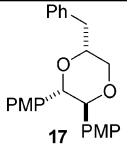
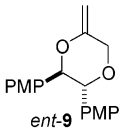
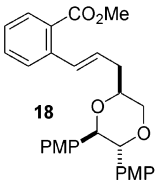
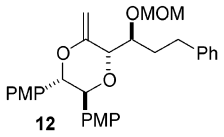
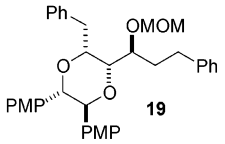
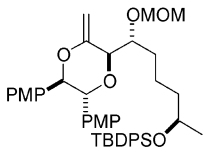
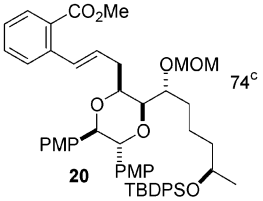
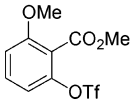
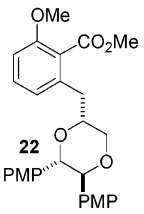
To make the approach more general, we turned our focus toward six-membered systems. In this regard, the glycolate derived oxapyrone **8**, developed by Andrus et al.,[18] seemed to be the substrate of choice. Not only are both the enantiomers of this auxiliary readily synthesized but also it affords 1,2-anti selective aldol addition products, and the PMP part can be removed very easily at a later stage to unmask the diol functionality in the product. The substrates for the key transformation were readily prepared in high yields by Petasis methylenation of the corresponding oxapyrones (Scheme 2). The *exo*-methylene compound **9** was

Scheme 2. Conversion of the Andrus Dioxanone to Exocyclic Enol Ethers Using the Petasis Reaction



used immediately after the olefination reaction. The other compounds (**12** and **16**) could be purified by chromatography on aluminum oxide. The results of our study with lactone **8** and derived enol ethers are collected in Table 1. Compound **11** was obtained by *anti*-aldol reaction of **8** with phenylpropanal followed by MOM protection. In a similar manner, **15** was prepared by the *anti*-aldol addition reaction of *ent*-**8** with aldehyde[19] **13** followed by MOM protection. Both aldol products **10** and **14** are prone to retro aldol reactions and are protected without further purification.

Table 1. Suzuki Cross-Coupling of the Exocyclic Enol Ethers Derived from the Dioxanone **8** and *ent*-**8**

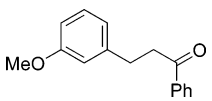
Entry	Enol ether	Halide/Triflate	Product[a]	%Yield
1		PhBr		72
2		5		87[b]
3		PhBr		76
4		5		74[c]
5[d]	9			53

[a] Enol ether (1 equiv, 0.33 M) in THF, 9-BBN (1.2 equiv), 0 °C, stir for 6 h at 23 °C; add this solution to a solution of halide/triflate (1.2 equiv), Ph_3As (0.05 equiv), Cs_2CO_3 (2 equiv), H_2O (30 equiv), $PdCl_2$(dppf) (0.05 equiv), 23 °C, 14−16 h; DMF. [b] $E/Z = 9:1$. [c] $E/Z = 10:1$. [d] In the presence of KBr (1.2 equiv).

Initial studies were carried out on substrates without a side chain (**9** and *ent*-**9**) (Table 1). The reactions afforded a single detectable diastereomer. The stereochemistry of the product is the result of a pseudoaxial attack of the borane to the double bond (structure **E**, Scheme 3) as could be shown by NMR studies. A clear indication of the stereochemical outcome is the coupling constant of 10.6 Hz for the axial−axial coupling for H-5 (structure **17**, Scheme 3).

An absolute proof for this was obtained by oxidative ether cleavage from **17** (Scheme 3). Thus, stirring of the dioxane

(17) From this reaction, the following phenone was isolated:



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(19) Haynes, R. K.; Lam, W. W. L.; Yeung, L.-L.; Williams, I. D.; Ridley, A. C.; Starling, S. M.; Vonwiller, S. C.; Hambley, T. W.; Lelandais, P. *J. Org. Chem.* **1997**, *62*, 4552−4553.

Scheme 3. Liberation of the Diol from the Dioxanes **17** and **18**

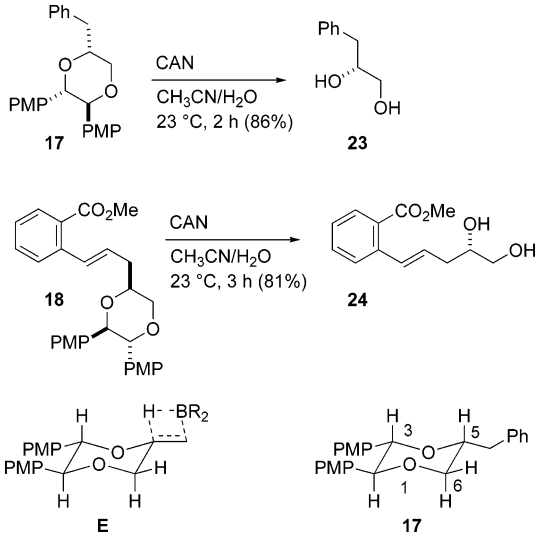
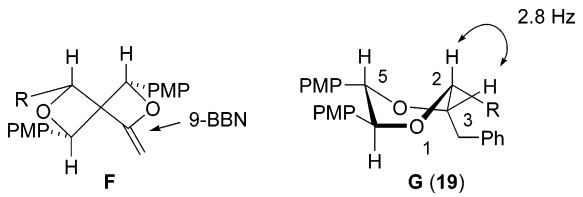


Figure 2. Possible twist-boat conformations of 2-substituted-3-methylidene-1,4-dioxanes and the derived hydroboration/cross-coupling products.



17 with CAN in a CH_3CN/H_2O system for 2 h afforded the diol **23** in 86% isolated yield. The optical rotation {$[\alpha]^{20}_D = +20.4$ (*c* 1.0 in $CHCl_3$), ref 20; $[\alpha]^{20}_D = +15.0$ (*c* 1.0 in $CHCl_3$), ref 21; $[\alpha]^{20}_D = -18.6$ (*c* 1.3 in $CHCl_3$) for *ent*-**23**} and the spectral characteristics for **23** were in complete agreement with that reported in the literature. The sign and value of the optical rotation undoubtedly proved the absolute configuration and enantiomeric excess of **23** and thereby that of **17**. It also allows a conclusion about the facial selectivity in the hydroboration step. Under similar conditions, the oxidative deprotection of compound **18** provided diol **24**. Given the ease of the liberation of the diol, this method affords synthetically useful enantiomerically pure diols which may be difficult to obtain by traditional methods.

As shown in Table 1, substrates with a side chain on C3 were also studied. According to ChemBats3D (8.0) calculations, these substrates with substituents on C3 adopt a twist-boat conformation with the *p*-methoxyphenyl groups occupying equatorial positions. Accordingly, the substituent in position 2 points in a pseudoequatorial direction. It is then obvious that the borane approaches from the convex face (cf. structure **F**). In the resulting products such as **19** or **20**, the 1,4-dioxane ring now shows a more or less distorted boat conformation. A clear indication of the stereochemical outcome is the coupling constant of 2.8 Hz for H-2/H-3 as in **19** (Figure 2). According to calculations, the dihedral angle between the vicinal hydrogens H-2 and H-3 in **19** is approximately 48° and the measured coupling constant is consistent with this angle. With vinyl iodides as substrates (Scheme 1, compound **6**; Table 1, entries 2 and 4), it was found that in the coupling products the *E*/*Z* ratio is higher than in the starting iodide. This is due to the much lower reactivity of the corresponding *Z*-vinyl iodides. In fact, if an excess (2 equiv) of the vinyl iodide was used (entry 4), the recovered vinyl iodide was enriched in the *Z*-isomer. Entry 5 shows that triflate[22] **21** can also be used in the coupling step.

In conclusion, we have developed a new and easy alternative for the synthesis of complex *anti*-1,2-diols by a tandem hydroboration/Suzuki coupling sequence of α-alkoxy enol ethers. An easily available glycolate-based chiral oxapyrone has been employed. The simplicity of the tandem reaction, the easy preparation of both enantiomers of the Andrus' chiral oxapyrone, and a straightforward cleavage procedure complement other methods for the synthesis of highly functionalized diols. This methodology has already been successfully employed by us in the synthesis of complex natural products, the results of which shall be reported soon.

Acknowledgment. Both authors, M.K. and A.K., contributed equally to this work. Financial support by the Deutsche Forschungsgemeinschaft and the Fonds der Chemischen Industrie is gratefully acknowledged. In addition, we acknowledge partial support by COST D28. M.K. thanks the Alexander von Humboldt foundation for a postdoctoral fellowship.

Supporting Information Available: Experimental procedures and characterization for all new compounds reported and copies of NMR spectra for important intermediates. This material is available free of charge via the Internet at http://pubs.acs.org.

OL0602194

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