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Desymmetrization of *meso-*1,3-Tetrols via Oxazaborolidine-Mediated Enantiotopic Group Selective Ring-Cleavage of Bisacetal Derivatives

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Abstract: Meso-1,3,5,7-heptanetetrol and -1,3,6,8-octanetetrol were desymmetrized via enantiotopic group selective ring-cleavage reaction of their bisacetal derivatives using a chiral oxazaborolidine. © 1998 Elsevier Science Ltd. All rights reserved.

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Two-direction chain extension and asymmetric desymmetrization of the resulting *meso* compound have recently emerged as an efficient strategy for the construction of multiple stereogenic centers [1,2]. The approach has been successfully employed in asymmetric syntheses of skipped and propionate-derived 1,3-polyols of potential σ -symmetry [2,3]. Although there is no precedent, enantiodifferentiating ring-cleavage of bisacetal derivatives is a straightforward method for desymmetrization of 1,3-polyols (Scheme 1). In the preceding paper, we reported an intermolecular differentiation of enantiomeric acetals through a chiral oxazaborolidine-mediated ring-cleavage reaction with a methallylsilane as a nucleophile [4]. Herein, we describe an application of the acetal-cleavage reaction to desymmetrization of *meso*-1,3-tetrol derivatives 4a,b.



For the synthesis of bisacetal 4a, hydroxy ester 1 was reduced under chelation-controlled conditions (Et₂BOMe, NaBH₄) [5] to give syn-diol 2 in 90% yield (eq 1). Protection of the hydroxy groups (PhCH(OMe)₂, TsOH) and LiAlH₄ reduction transformed 2 into mono-acetal 3 (81%). Deprotection of 3 (H₂, Pd/C) followed by acetalization with benzaldehyde (TsOH, benzene, reflux) furnished a crystalline bisacetal 4a (mp 91-92 °C) in 63% yield. Bisacetal 4b was prepared starting from succinaldehyde derivative 5 (eq 2). 1,4-Asymmetric induction developed by Molander et al. [6] was successfully applied to the double allylation of 5 (allyltributyltin, TMSOTf), affording stereoselectively (meso:dl = 9:1) meso product 6 (mp 42-43 °C) in 75% yield. Oxidative cleavage (OsO₄, NMO, NaIO₄) and subsequent NaBH₄ reduction converted 6 into 7 (69%). After deprotection (H₂, Pd/C) and acetalization of the resulting tetrol with benzaldehyde, bisacetal 4b (mp 103-103.5 °C) was



isolated in 44% yield.

Ring-cleavage of bisacetal 4a was examined by using N-mesyloxazaborolidine 8 (1.0 equiv) as a chiral Lewis acid and methallylsilane 9 (1.5 equiv) as a nucleophile in anticipation of an enantiodifferentiating reaction on the (S)-acetal moiety (eq 3) [4]. When the reaction was carried out in CH₂Cl₂ at -50 °C for 12 h, the mono-cleavage product 10a was obtained as a mixture of diastereomers in 94% yield together with a small amount of the corresponding bis-cleavage product (< 5%). After protection of the hydroxy group as a pivalate (84%), the 3-methyl-1-phenyl-3-butenyl group was removed in two steps (75%) to give O-benzylidene pivalate 11a. Enantiomeric purity of 11a was determined to be 88% ee based on the ¹H NMR analysis of the MTPA ester derivative. The absolute configuration of 11a, established by the modified Mosher's method [7], was in accord with the anticipated reaction on the (S)-acetal moiety of 4a.

Ring-cleavage of 4b under similar conditions afforded the mono-cleavage product 10b (82%) together with the bis-cleavage product (15%). Formation of the bis-cleavage product in relatively large amount suggested a higher ee of mono-cleavage product 10b through the kinetic resolution in the second bond cleavage [8]. Indeed, after conversion into O-benzylidene pivalate 11b (63% overall yield), the ¹H NMR analysis of the MTPA ester derivative established the high ee of 95%¹ as well as the absolute configuration.²

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- 1. Ring-cleavage of 4b using 8 (0.5 equiv) and 9 (0.75 equiv) at -50 °C for 8 h gave 10a (87% ee) in 58% yield together with the recovery of 4b (37%).
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