

products by flash chromatography, afforded the desired, peracylated pseudodisaccharide 11 as well as a substantial amount of its *C*-pyranosyl/*C*-furanosyl isomer (ratio of ring-size isomers: 55:45, 49.5% overall yield); both were obtained as *R/S* mixtures at C-7. In order to get rid of the pivaloyl group, and thus convert 11 into a pseudo-symmetric structure, compound 11 was deacylated and reacylated (54% for both steps) to give the remarkable pseudodisaccharide 12 which bears two identical gluco-pyranosyl units [syrup;  $[\alpha]_{\text{D}}^{20} -5.3^\circ$  (*c* 1.5,  $\text{CHCl}_3$ )]; as a result of the presence of the nitro group at C-7 (pseudoasymmetric center), the two sugar units are, however, diastereotopic, and the  $^1\text{H}$  NMR parameters of 12<sup>17</sup> provide, thus, direct evidence on the conformation about the interglycosidic linkages: the magnitude of the  $J_{7,1}$  and  $J_{7,1'}$  coupling constants<sup>17</sup> indicates a nearly anti relationship between H-1 and H-7, and *gauche* between H-1' and H-7, which is consistent with the sterically most favorable conformation of 12 about C-1-C-7 and C-1'-C-7 (see 12 in Scheme II); this conformation (equivalent to standard torsional angles in disaccharides<sup>18</sup>  $\phi, \psi = -60^\circ, -60^\circ$ ) is essentially the same as the one predicted to be the most stable for  $\beta, \beta$ -trehalose and model compounds.<sup>19</sup>

(17) Selected  $^1\text{H}$  NMR data ( $\text{CDCl}_3$ )  $\delta$  4.71 (dd, 1 H,  $J_{7,1} = 8.2, J_{7,1'} = 2.9$  Hz, H-7), 4.41 (dd, 1 H,  $J_{1,2} = 9.7$  Hz, H-1), 4.19 (dd, 1 H,  $J_{1',2'} = 10.5$  Hz, H-1').

(18) Stoddart, J. F. *Stereochemistry of Carbohydrates*; Wiley-Interscience: New York, 1971.

Removal of the nitro group of 12 using  $\text{Bu}_3\text{SnH}$  afforded the symmetric  $\beta, \beta$ -trehalose analogue 13<sup>20</sup> [76%; mp 141.4-142.4 °C;  $[\alpha]_{\text{D}}^{20} -17.2^\circ$  (*c* 1.5,  $\text{CHCl}_3$ )], the first example of a (1→1)-linked *C*-disaccharide related to trehalose. Interestingly, the specific rotation of 13 was found to be identical with that measured and reported<sup>21</sup> in 1909 by E. Fischer for  $\beta, \beta$ -trehalose octaacetate! Detailed structural studies on these and related pseudodisaccharides are in progress and will be reported separately.

The results described in this paper demonstrate that the nitroaldol reaction of a  $\beta$ -*C*-glycosylnitromethane derivative with *aldehydo* sugars provide a simple means of achieving the synthesis of  $\beta$ -(1→6)- and  $\beta, \beta$ -(1→1)-linked *C*-disaccharides with *minimal functional group manipulation*.

**Acknowledgment.** Financial support from the National Institutes of Health (Grant DK-35766) is gratefully acknowledged.

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(20)  $^{13}\text{C}$  NMR (90 MHz,  $\text{CDCl}_3$ ):  $\delta$  20.54 (2 C), 20.63, 20.67 ( $\text{CH}_3\text{CO}$ 's), 33.34 (0.5 C, C-7), 62.53 (C-6), 68.92, 71.96, 73.25, 74.38, 76.02 (C-1-C-5), 169.42, 169.63, 170.22, and 170.42 ( $\text{CH}_3\text{CO}$ 's).  $^1\text{H}$  NMR (360 MHz,  $\text{CDCl}_3$ ):  $\delta$  1.60 (m, 1 H, apparent  $J_{7,1} = 5.4$  and 7.6 Hz, H-7's), 1.99, 2.03, 2.05, and 2.10 (4 s, 4 × 3 H,  $\text{CH}_3\text{CO}$ 's), 3.60 (ddd, 1 H,  $J_{4,5} = 10.0, J_{5,6A} = 2.4, J_{5,6B} = 5.35$  Hz, H-5), 3.70 (ddd, 1 H,  $J_{1,2} = 10.0$  Hz, H-1), 4.10 (dd, 1 H,  $J_{6A,6B} = 12.25$  Hz, H-6A), 4.22 (dd, 1 H, H-6B), 4.85 (t, 1 H,  $J_{2,3} = 9.2$  Hz, H-2), 5.03 and 5.20 (2 t, 2 × 1 H,  $J_{3,4} \sim 9.5$  Hz, H-3 and H-4).

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## Reduction of $\beta$ -Hydroxy Ketones with Catecholborane. A Stereoselective Approach to the Synthesis of Syn 1,3-Diols

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**Summary:** The stereoselective reduction of acyclic  $\beta$ -hydroxy ketones to syn 1,3-diols may be achieved with the mild reducing agent catecholborane. In certain instances reaction stereoselectivity may be enhanced through rhodium(I) catalysis.

The reduction of acyclic  $\beta$ -hydroxy ketones in a predictable and stereoselective manner is of considerable current interest, since syn and anti 1,3-diols are recurring units in a variety of polyacetate- and polypropionate-derived natural products. From the accumulated body of data, several generalizations have emerged. For example, when the reducing agent possesses the capacity to bind to the hydroxyl function with *intramolecular transfer of hydride*, the anti 1,3-diol is formed preferentially (eq 1).<sup>1</sup> In contrast, when an additive (e.g.,  $\text{Et}_2\text{B-X}$ ) is employed to preorganize the substrate prior to *intermolecular hydride addition* (e.g., by  $\text{NaBH}_4$ ), the syn isomer becomes the major product (eq 2).<sup>2</sup> In the present paper, we report

an operationally convenient method for the syn-selective reduction of  $\beta$ -hydroxy ketones which complements the existing methods. In these reactions, catecholborane (CB) apparently serves both to provide substrate organization through boron aldolate formation and to function as the hydride donor.<sup>3</sup>

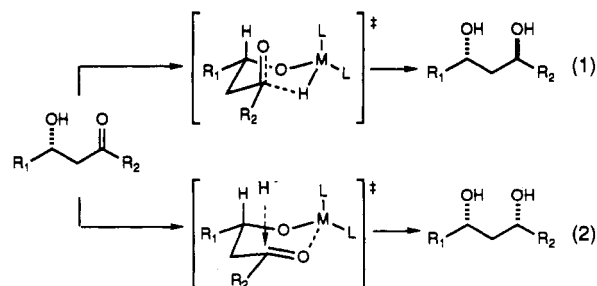
Several representative experiments serve to illustrate the dual role which catecholborane might be assuming in these reactions. Treatment of the  $\beta$ -hydroxy ketone 1 (Table I, entry 1) with 2.2 equiv of catecholborane in THF<sup>4</sup> (-10 °C, 90 min) affords the syn diol 2 in 82% yield

(2) For syn-selective reductions of  $\beta$ -hydroxy ketones, see: (a) Hanamoto, T.; Hiyama, T. *Tetrahedron Lett.* 1988, 29, 6467-6470. (b) Chen, K.-M.; Hardtmann, G. E.; Prasad, K.; Repic, O.; Shapiro, M. J. *Chem. Lett.* 1987, 1923-1926. (c) Bonadies, F.; DiFabio, R.; Gubioti, A.; Mecozzi, S.; Bonini, C. *Tetrahedron Lett.* 1987, 28, 703-706. (d) Kiyooka, S.; Kuroda, H.; Shimasaki, Y. *Tetrahedron Lett.* 1986, 27, 3009-3112. (e) Kathawala, F. G.; Prager, B.; Prasad, K.; Repic, O.; Shapiro, M. J.; Stabler, R. S.; Widler, L. *Helv. Chim. Acta* 1986, 69, 803-805. (f) Narasaka, K.; Pai, F.-C. *Tetrahedron* 1984, 40, 2233-2238. (g) Narasaka, K.; Pai, F.-C. *Chem. Lett.* 1980, 1415-1418.

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(4) Reductions may be performed in  $\text{CH}_2\text{Cl}_2$  as well as THF. For example, 1 is reduced to the corresponding syn diol in  $\text{CH}_2\text{Cl}_2$  (80% yield, syn:anti = 10:1).

(1) For anti-selective reductions of  $\beta$ -hydroxy ketones, see: (a) Evans, D. A.; Hoveyda, A. H. *J. Am. Chem. Soc.*, in press. (b) Evans, D. A.; Chapman, K. T.; Carreira, E. M. *J. Am. Chem. Soc.* 1988, 110, 3560-3578. (c) Anwar, S.; Davis, A. P. *Tetrahedron* 1988, 44, 3761-3770.



(syn:anti = 10:1).<sup>5,6</sup> On the other hand, the  $\beta$ -*tert*-butyldimethylsilyl ether derived from 1 affords only a 2:1 ratio of syn:anti diastereomers (85% yield) under the same conditions. The presumption that boron aldolate formation precedes the reduction step was reinforced by the observation that upon exposure of 1 to only 1.1 equiv of the boron hydride less than 10% reduction was effected. These findings are fully consistent with the projection that 1 equiv of the boron hydride is rapidly consumed in the formation of the aldol boronate and the second equivalent of CB serves as the hydride source to effect the stereoselective reduction. Given the stereoselectivity observed in the preceding reaction, it was somewhat surprising that the analogous reduction of ketone 3 proceeded with lower diastereoselectivity (syn:anti = 3:1; 92% yield). Since the preceding experiments indicate that the reaction appears to occur in a less stereoselective fashion in the absence of internal chelation, it is likely that the less encumbered ketone 3 may be reduced directly at a rate competitive with formation of the boronic ester. In accordance with this proposal, we have discovered, *vide infra*, that in reductions of substrates 1 and 3, enhancement of the rate of H<sub>2</sub> evolution greatly improves the levels of diastereoselection (Table II).

The incorporation of a methyl substituent between the carbonyl and hydroxyl groups can either reinforce or diminish the intrinsic syn diastereoselectivity, depending upon the stereochemical relationship between the two substituents. For example, the syn and anti  $\alpha$ -methyl- $\beta$ -hydroxy ketones 5 and 7 are transformed to their corresponding syn diols 6 and 8 (-10 °C, 5 h) with 5 equiv of CB (Table I, entries 3, 4). The difference in stereoselectivity observed in the reduction of 5 (35:1) and 7 (6:1) may be rationalized by the imposition of the reinforcing syn methyl group in 5 which enhances the facial bias imposed by the  $\beta$ -oxygen chelate. It is noteworthy that the anti methyl substituent in 7 diminishes, but does not override, the diastereofacial bias imparted by the  $\beta$ -substituent.<sup>7</sup>

(5) A typical experimental procedure is as follows: The  $\beta$ -hydroxy ketone 9 (135 mg, 0.54 mmol) is dissolved in 4.0 mL of anhydrous THF in a dry round-bottomed flask under N<sub>2</sub>. The solution is chilled in a MeOH-ice bath (-10 °C) and charged with 255  $\mu$ L (2.70 mmol) of freshly distilled catecholborane. After 5 h, the reaction mixture is quenched by the addition of 2.0 mL of anhydrous MeOH and 2.0 mL of a saturated aqueous solution of sodium potassium tartrate. This mixture is allowed to stir at 25 °C for 2 h, and the desired product is isolated by a standard extractive isolation procedure. Silica gel chromatography (4:1 hexane-diethyl ether) affords 115 mg (0.46 mmol, 85% yield) of 10 as a colorless oil. GLC analysis of the corresponding diacetate and comparison with authentic samples indicate an 80:1 ratio in favor of the syn diastereomer.

(6) The stereochemical identity of all the products reported herein has been determined through comparison with authentic syn and anti diastereomers and by analysis of <sup>1</sup>H NMR coupling constants and nuclear Overhauser experiments on the formal or acetonide derivatives. See the supplementary material for details.

(7) The dependence of stereoselection on the substitution and stereochemical pattern of substrates described here generally parallels that observed in reductions of these and similar substrates mediated by Et<sub>3</sub>B and NaBH<sub>4</sub> as reported by Narasaka and co-workers.<sup>2f</sup> However, with anti  $\alpha$ -alkyl- $\beta$ -hydroxy ketones, where the  $\alpha$ -substituent is a butyl or phenyl group, these workers report that anti diols are formed predominantly.

**Table I. Reduction of  $\beta$ -Hydroxy Ketones by Catecholborane<sup>a</sup>**

entry	substrate	product	yield <sup>b</sup> (syn:anti) <sup>c</sup>
1			82% (10:1)
2			92% (3:1)
3			82% (35:1)
4			77% (6:1)
5			85% (80:1)
6			93% (6:1)
7			82% (9:1)

<sup>a</sup> In the reactions shown in entries 1 and 2, 2.2 equiv of CB were used; in all other runs, 4–5 equiv of CB were employed. All reactions were performed at -10 °C. <sup>b</sup> Isolated yields of purified products. <sup>c</sup> Ratios were measured by GLC.

**Table II. Effect of Rh(PPh<sub>3</sub>)<sub>3</sub>Cl on Stereoselectivity**

substrate	temp	additive	yield <sup>b</sup> (syn:anti) <sup>c</sup>
	-10 °C	None	82% (10:1)
	-10 °C	5% Rh(I) <sup>d</sup>	76% (12:1)
	-35 °C	None	87% (6:1)
	-35 °C	5% Rh(I) <sup>d</sup>	86% (20:1)
	-10 °C	None	92% (3:1)
	-10 °C	5% Rh(I) <sup>d</sup>	93% (10:1)
	-10 °C	None	77% (6:1)
	-10 °C	5% Rh(I) <sup>d</sup>	66% (6:1)

<sup>a-c</sup> See Table I. <sup>d</sup> RhCl(PPh<sub>3</sub>)<sub>3</sub>.

Subtle steric effects were found to have a surprising effect on the overall level of stereocontrol. For example, whereas reaction of the  $\alpha,\beta$ -unsaturated ketone 9 (Table I, entry 5) proceeds with excellent diastereoselectivity (syn:anti = 80:1), the related saturated ketones 11 and 13 afforded a 6:1 and a 9:1 ratio of isomers, respectively (entries 6, 7). We project that the lower levels of facial selectivity observed in the reduction of 11 and 13 may be tied to the conformational disposition of the exocyclic isopropyl substituent in the chelated intermediate. This moiety may adopt a conformation reinforced to avoid a syn pentane interaction with the  $\alpha$ -methyl substituent and thus hinders hydride attack from the syn diastereoface.

A systematic variation in reaction conditions was examined in an effort to enhance reaction diastereoselection

(Table II). Lower temperatures were found to have a deleterious effect on the stereochemical outcome of these reductions. It is possible that a decrease in reaction temperature retards the rate of H<sub>2</sub> evolution and boronic ester generation, but has a weaker influence on the rate of the hydride addition, and thus leads to diminished diastereocontrol. Since we had independently made the observation that Wilkinson's catalyst strongly accelerates borate ester formation between alcohols and catecholborane, we evaluated the effect of this catalyst on reaction stereoselectivity (Table II). Accordingly, in the presence of 5% of the rhodium catalyst under otherwise identical conditions (-35 °C), ketone **1** is reduced with 20:1 syn selectivity, and the stereoselection in the reduction of **3** is improved from 3:1 to 10:1. The positive influence of the catalyst on the reaction stereoselection may be attributed, at least in

part, to the ability of the transition-metal complex to catalyze the formation of the boronic ester.

In summary, catecholborane is an effective reagent for the syn-selective reduction of  $\beta$ -hydroxy ketones; in certain cases, the levels of diastereoselection can be improved by catalytic amounts of Rh(PPh<sub>3</sub>)<sub>3</sub>Cl. It is anticipated that the mildness and convenience of this reaction will render it a useful method in synthesis.

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**Supplementary Material Available:** Experimental data for compounds described in this paper (3 pages). Ordering information is given on any current masthead page.

## Studies Directed toward the Total Synthesis of Lonomycin A (Emericid). Asymmetric Synthesis of the C<sub>1</sub>-C<sub>11</sub> Synthone

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**Summary:** The asymmetric synthesis of the lonomycin A C<sub>1</sub>-C<sub>11</sub> synthon **2** is described, in which the absolute stereochemical relationships were established through the use of  $\beta$ -keto imide aldol bond constructions, internally directed  $\beta$ -hydroxy ketone reduction, and diastereoselective rhodium-catalyzed hydroboration.

Lonomycin A, also known as emericid, is one of the most structurally complex of the polyether antibiotics isolated to date.<sup>1</sup> In addition to the 23 resident stereogenic centers, the latent instability of the carboxyl terminus of this ionophore renders lonomycin a substantial challenge as a target for synthesis. In this paper, we describe the successful construction of the C<sub>1</sub>-C<sub>11</sub> polypropionate portion of this molecule (structure **2**, Scheme I). Recent methodology developed in this laboratory for the assemblage of polypropionate structures utilizing chiral  $\beta$ -keto imides<sup>2</sup> has been exploited to control all pivotal stereochemical relationships and C-C bond constructions in the synthesis of **2**.

The initial stages of the synthesis are illustrated in Scheme II. All absolute stereochemical control in this sequence is ultimately derived from the Sn(II) enolate of  $\beta$ -keto imide **4**. Stannous triflate mediated aldol coupling between **4** and methacrolein (Sn(OTf)<sub>2</sub>, Et<sub>3</sub>N, **4**, CH<sub>2</sub>Cl<sub>2</sub>, -20 °C, 1 h; 3-5 equiv of RCHO, -78 °C, 30 min) provided adduct **5** (78%, de = 90%). Subsequent anti reduction<sup>3</sup> of the  $\beta$ -hydroxy ketone (NaBH(OAc)<sub>3</sub>, HOAc, 25 °C, 1 h) provided diol **6** (93%, de = 94%). Refunctionalization to aldehyde **7** was achieved by the straightforward sequence of acetonide formation (2,2-dimethoxypropane,

Dowex-50, CH<sub>2</sub>Cl<sub>2</sub>, 25 °C, 1 h), LiAlH<sub>4</sub> reduction of the carboximide (THF, -78 °C, 1 h), and reoxidation using the technique of Parikh and Doering<sup>4</sup> (SO<sub>3</sub>py, DMSO/CH<sub>2</sub>Cl<sub>2</sub>, -5 °C, 1 h) in 80% overall yield. A second  $\beta$ -keto imide aldol reaction between **4** and aldehyde **7** (2 equiv each Sn(OTf)<sub>2</sub>, Et<sub>3</sub>N, and **4**, CH<sub>2</sub>Cl<sub>2</sub>, -20 °C, 1 h; 1 equiv **7**, -78 °C, 30 min) provided **8** (79% yield), which contains all of the carbon atoms and seven of the eight asymmetric centers present in the C<sub>1</sub>-C<sub>11</sub> synthon. It is noteworthy that the required stereochemical relationship of the labile C<sub>2</sub> methyl group is also secured in this synthesis plan.

At this point we faced the task of methylating the aldol adduct **8** without promoting retro-aldol cleavage or epimerization of the C<sub>2</sub> methyl-bearing stereocenter. The use of methyl triflate (15 equiv, 30 equiv 2,6-di-*tert*-butylpyridine, CDCl<sub>3</sub>, 80 °C, 4 h) proved to be an efficient solution to this problem,<sup>5</sup> providing **9** in 83% yield. It was gratifying that no detectable C<sub>2</sub> diastereomization occurred during this methylation, even when the reaction mixture was heated at reflux in chloroform for an extended time period. The success of this transformation is a testament to the stability imparted to the  $\beta$ -keto imide stereocenter by allylic strain control elements.<sup>6</sup>

To complete the preparation of **2**, we hoped to introduce the C<sub>10</sub> stereocenter through a rhodium-catalyzed hydroboration<sup>7</sup> which would also serve to introduce the required oxygenation at C<sub>11</sub> needed for eventual aldol coupling to

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