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Stereoselective Synthesis of 1,3-*anti* Diols by an Ipc-Mediated Domino Aldol-Coupling/Reduction Sequence

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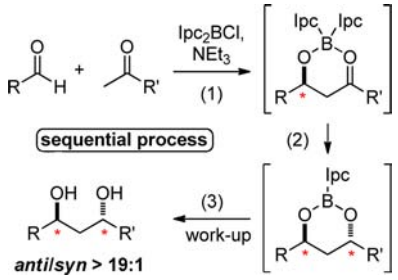
ABSTRACT



A novel domino process for 1,3-*anti* diol synthesis by the union of a methyl ketone with an aldehyde is described. The operationally simple procedure is based on an Ipc-boron-aldol coupling and subsequent Ipc-mediated reduction of the intermediate β-hydroxy-ketone. The sequence proceeds with excellent *anti*-selectivities and enables the rapid construction of complex polyketide fragments.

The 1,3-diol motif represents a ubiquitous structural feature in numerous natural products, particularly among polyketides, as well as bioactive agents and pharmaceuticals,[1] rendering the development of efficient methods for their synthesis an important research goal. Undoubtedly, the aldol reaction and subsequent reduction of the derived β-hydroxy-ketones constitutes one of the most powerful and versatile synthetic procedures for the preparation of this prevalent synthon.[2] However, as shown in Scheme 1 (top part), this approach usually requires two separate synthetic steps, i.e., a C−C bond formation (*viz* coupling product **A**) and a reduction (i.e., transformation of **A** to **B**).[3,4] From the perspective of step economy, a more direct combination of these two transformations in a domino type fashion by suitable reagent design would be highly desirable. As part of our efforts to develop new sequential processes for polyketide synthesis,[5] we report a domino aldol/reduction sequence that enables a highly stereoselective access to 1,3-*anti* diols by an operationally simple procedure that may be readily applied in complex polyketide synthesis.

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(1) (a) Cragg, G. M.; Newman, D. J. *Cancer Invest*. **1999**, *17*, 153. (b) Demain, A. L. *Biotechnol. Adv*. **2000**, *18*, 499. (c) Weissman, K. J.; Müller, R. *Nat. Prod. Rep*. **2010**, *27*, 1276.

(2) (a) Kim, B. M.; Williams, S. F.; Masamune, S. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Heathcook, C. H., Eds.; Pergamon: Oxford, 1991; Vol. 2, p 229. (b) Yeung, K.-S.; Paterson, I. *Chem. Rev*. **2005**, *105*, 4237. (c) Schetter, B.; Mahrwald, R. *Angew. Chem., Int. Ed*. **2006**, *45*, 7506. (d) Brodmann, R.; Lorenz, M.; Schäckel, R.; Simsek, S.; Kalesse, M. *Synlett* **2009**, 174. (e) Li, J.; Menche, D. *Synlett* **2009**, 2293.

(3) For 1,3-*syn* reduction of β-hydroxy ketones, see: (a) Chen, K.-M.; Hardtmann, G. E.; Prasad, K.; Repic, O.; Shapiro, M. J. *Tetrahedron Lett*. **1987**, *28*, 155. (b) Evans, D. A.; Hoveyda, A. H. *J. Org. Chem*. **1990**, *55*, 5190. For 1,3-*anti* reduction of β-hydroxy ketones, see: (c) Anwar, S.; Davis, A. P. *Tetrahedron* **1984**, *40*, 2233. (d) Evans, D. A.; Chapman, K. T.; Carreira, E. M. *J. Am. Chem. Soc*. **1988**, *110*, 3560. (e) Evans, D. A.; Hoveyda, A. H. *J. Am. Chem. Soc*. **1990**, *112*, 6447.

(4) The Paterson group described a one-pot method for boron-aldol reactions and subsequent reduction of the intermediate β-oxo-boron-aldolate by addition of a suitable reducing agent to afford the corresponding 1,3-*syn* diols: (a) Paterson, I.; Perkins, M. V. *Tetrahedron* **1996**, *52*, 1811. (b) Paterson, I.; Wren, S. P. *J. Chem. Soc., Chem. Commun*. **1993**, 1790.

(5) (a) Wang, L.; Li, P.; Menche, D. *Angew. Chem., Int. Ed*. **2010**, *49*, 9270. (b) Morgen, M.; Bretzke, S.; Li, P.; Menche, D. *Org. Lett*. **2010**, *12*, 4494. (c) Wang, L.; Menche, D. *Angew. Chem., Int. Ed*. **2012**, *51*, 9425. (d) Debnar, T.; Dreisigacker, S.; Menche, D. *Chem. Commun*. **2013**, *49*, 725.

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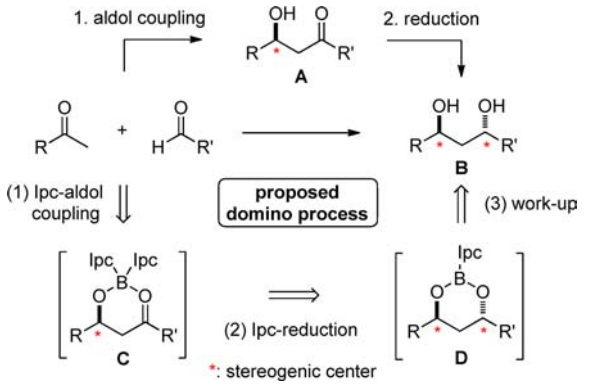
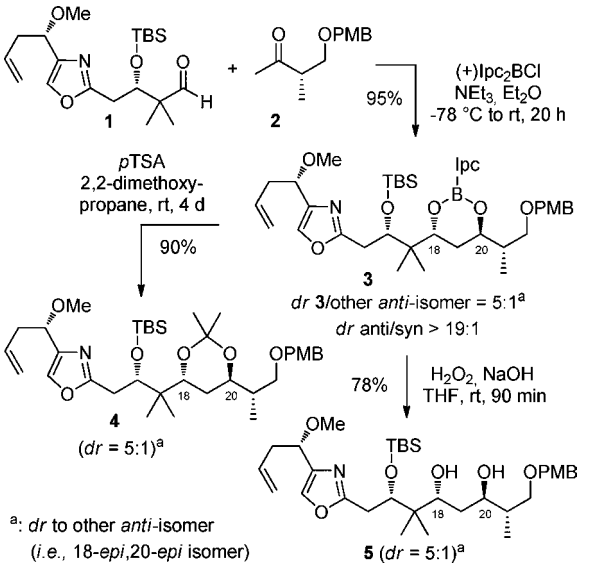
Scheme 1. Domino Concept for Direct 1,3-Diol Synthesis



Auxiliary-controlled aldol reactions play an important role in introducing stereoselectivity, and among these, the use of chiral isopinocampheyl (Ipc) boron enolates has emerged as a powerful tool in the construction of both complex polyacetates and polypropionates.[6] Importantly, this chiral auxiliary may be installed in an intermediate fashion to various ketones, which adds to the unique efficiency of this reagent. Motivated by the intrinsic ability of the Ipc-residue to act likewise as a reducing agent,[7] we envisioned that a suitable reaction design might enable a combination of these processes in a one-pot fashion. Consequently, as shown in Scheme 1, our synthetic concept capitalizes on a three-step sequential process involving an Ipc-aldol reaction between a methyl ketone and an aldehyde (1) resulting in the corresponding boron-aldolate **C**, which might then undergo an intramolecular Ipc-mediated reduction to cyclic boronate **D** (2) and then generate the desired 1,3-diol motif during workup in a highly concise fashion (3). Notably, two new stereogenic centers are assembled along this process, demonstrating a high increase in structural complexity from very simple starting materials.

For realization of this concept we studied the challenging aldol coupling of aldehyde **1** and methyl ketone **2** (Scheme 2) within our synthetic campaign directed toward the polyketide rhizopodin.[8] To enhance the reactivity of the hindered aldehyde **1** as well as to simultaneously enable an Ipc-induced reduction, this coupling was evaluated at more elevated temperatures as compared to those conventionally used for this type of boron mediated aldol coupling.[6] This approach proved to be indeed successful. By raising the temperature to 25 °C, a clean conversion to cyclic boronate **3** was observed. This reduced product was obtained in high yields (95%).[9,10] Importantly, detailed structural analysis revealed that out of the four possible stereoisomeric products, only the two *anti*-isomers could be detected by NMR, viz. **3** and the other *anti*-isomer [i.e., (18-*epi*, 20-*epi*)-**3**, not shown]. The stereochemistry of both isomers was assigned by NMR methods[11] and confirmed by transformation into acetonide **4**. Finally, the structure was proven by oxidative removal of the boronate[12] and comparison of the obtained diol **5** with material independently synthesized in our group.[8a]

Scheme 2. One-Pot Coupling of Ketone **1** with Aldehyde **2**



As shown in Table 1, various aldehydes (**6**–**10**)[13] and methyl ketones (**2**, **11**, and **12**) were then submitted to this domino sequence and both Ipc-isomers were used to study the influence of this chiral auxiliary on the stereochemical outcome of the reduction process. As expected, the coupling of aldehyde **6** as a structurally closely related homologue to **1** (Scheme 2) with methyl ketone **2** resulted in very similar degrees of selectivity and yield (entry 1). An analogous coupling with (−)-DIPCl afforded the same *anti*-product **13**, again with excellent *anti*/*syn* selectivities, albeit lower asymmetric induction in the initial aldol coupling, suggesting pronounced substrate control in this

(6) Cowden, C. J.; Paterson, I. *Org. React.* **1997**, *51*, 1.

(7) (a) Midland, M. M.; Greer, S.; Tramantano, A.; Zderic, S. A. *J. Am. Chem. Soc.* **1979**, *101*, 2352. (b) Brown, H. C.; Chandrasekharan, J.; Ramachandran, P. V. *J. Am. Chem. Soc.* **1988**, *110*, 1539. (c) Brown, H. C.; Ramachandran, P. V. *Acc. Chem. Res.* **1992**, *25*, 16. (d) Ramachandran, P. V.; Lu, Z.-H.; Brown, H. C. *Tetrahedron Lett.* **1997**, *38*, 761.

(8) (a) Dieckmann, M.; Kretschmer, M.; Li, P.; Rudolph, S.; Herkommer, D.; Menche, D. *Angew. Chem., Int. Ed.* **2012**, *51*, 5667. (b) Dieckmann, M.; Rudolph, S.; Dreisigacker, S.; Menche, D. *J. Org. Chem.* **2012**, *77*, 10782. (c) Kretschmer, M.; Menche, D. *Org. Lett.* **2012**, *14*, 382.

(9) Boronate **3** was shelf-stable under air at ambient temperature for months and showed similar TLC properties as the starting aldehyde **1**.

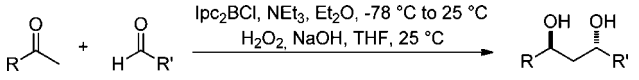
(10) In analogous reactions with Ipc_2BOTf only decomposition of the starting material was observed, possibly due to the higher Lewis acidity of this reagent under these conditions.

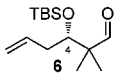
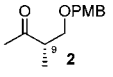
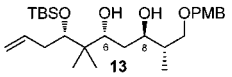
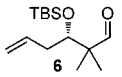
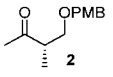
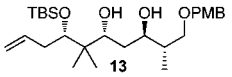
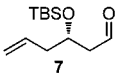
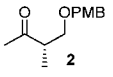
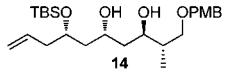
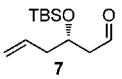
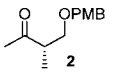
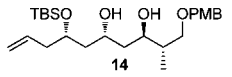
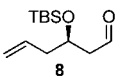
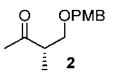
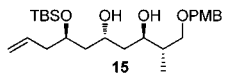
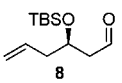
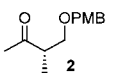
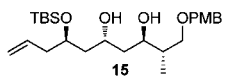
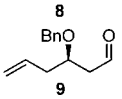
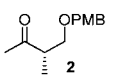
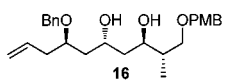
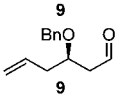
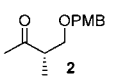
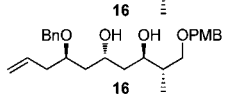
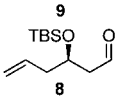
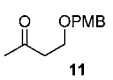
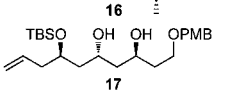
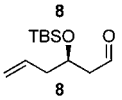
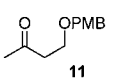
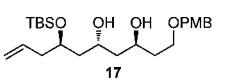
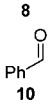
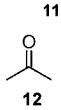
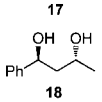
(11) The stereochemistry was assigned by NOE correlations and characteristic ^{13}C NMR signals of the acetonide moiety together with comparison of the NMR data of the product obtained by an analogous aldol coupling and an 1,3-*anti* reduction using the Evans–Carreira procedure: See ref 3d.

(12) In accordance with the high steric hindrance of this specific substrate, treatment with H_2O_2/NaOH (25 °C, 90 min) was required for oxidative cleavage, while no reaction was observed at neutral pH (H_2O_2/MeOH/buffer pH = 7, 25 °C, 2 h).

(13) The aldehyde substrates **6**–**9** were synthesized using Krische's allylation strategy: Hassan, A.; Lu, Y.; Krische, M. J. *Org. Lett.* **2009**, *11*, 3112. For details, see the SI.

Table 1. Scope of the Ipc-Mediated Domino Aldol Coupling/Reduction



entry	aldehyde	ketone	Ipc	product	yield [%][a]	*dr* to other *anti*-isomer (not shown)[b]	*dr* (*anti*/*syn*)[b]
1	 **6**	 **2**	(+)-Ipc	 **13**	75 (95)	6:1	> 19:1
2	 **6**	 **2**	(−)-Ipc	 **13**	42 (63)	2:1	> 19:1
3	 **7**	 **2**	(+)-Ipc	 **14**	82 (95)	3:1	> 19:1
4	 **7**	 **2**	(−)-Ipc	 **14**	49 (60)	1:1	> 19:1
5	 **8**	 **2**	(+)-Ipc	 **15**	85 (95)	10:1	> 19:1
6	 **8**	 **2**	(−)-Ipc	 **15**	43 (57)	2.5:1	> 19:1
7	 **9**	 **2**	(+)-Ipc	 **16**	95 (95)	>19:1	> 19:1
8	 **9**	 **2**	(−)-Ipc	 **16**	95 (95)	6:1	> 19:1
9	 **8**	 **11**	(+)-Ipc	 **17**	68	3:1	> 19:1
10	 **8**	 **11**	(−)-Ipc	 **17**	66	2:1	> 19:1
11	 **10**	 **12**	(−)-Ipc	 **18**	85	1.6:1	> 19:1

[a] Isolated yields after oxidative workup (H_2O_2/NaOH, 25 °C); yields in parentheses correspond to yields of cyclic boronates of type **D** (see Scheme 1); see also ref 14 and the Supporting Information (SI). [b] Stereochemistry and selectivity were assigned by the following methods: entries 1, 3, 5, 7: (H6/H8) NOESY-NMR correlations between H6 and H8 of cyclic boronate **D**; entries 1, 5: (H8/H9) NOESY-NMR correlations of the respective PMP-acetal; entries 2, 4, 6, 8, 10: comparison of NMR data with the cyclic boronate **D** and 1,3-diol from the experiment using (+)-Ipc_2BCl under otherwise identical conditions; entry 9: (H6/H8) NOESY-NMR correlations of the respective acetonide; entry 11: HPLC (AD-H) analysis, measurement of the optical rotation value and comparison with literature data.[17] The *anti*/*anti*-products were obtained as mixtures of diastereomers, which were not separable by column chromatography on silica gel; see SI.

specific aldol coupling, which cannot be overturned by the chirality of the Ipc-ligand used. To evaluate the potentially critical influence of the *gem*-dimethyl center of aldehydes **1** and **6**, a range of sterically less hindered aldehydes were evaluated (**7**–**9**). In all cases, the 1,3-*anti* diol products (**14**–**17**) were efficiently obtained, without the necessity of adopting additional reaction parameters, which clearly demonstrates that a sterically congested aldehyde is not required for this domino process.[14] The observed selectivities for the initial Ipc-mediated aldol coupling are in agreement with previously described examples.[6,15] In detail, very high selectivities in the initial C–C bond forming reaction were obtained in cases with a matched stereoinduction, e.g., entries 5 and 7, which additionally benefit from a 1,3-*anti*-induction from aldehydes **8**/**9** and a 1,4-*syn*-induction of methyl ketone **2**.[16] Along these lines, the remarkable influence of the type of protective group on the

(14) The oxidative cleavage of cyclic boronates **D** (Scheme 1) has not been optimized within this study. Steric demand as in the case of substrates **6**–**8** (Table 1) required treatment with H_2O_2/NaOH (25 °C, 2 h) to liberate the respective 1,3-*anti* diol, which decreased the yield due to partial TBS-cleavage (entries 1–6, 9, and 10). Sterically less burdened cyclic boronates such as those derived from benzyl protected aldehyde **9** could be cleaved much faster and without decomposition (entries 7, 8, and 11). To guarantee reproducibly high yields, an aqueous workup prior to the oxidative cleavage proved beneficial.

(15) Similar selectivities were observed in the corresponding direct aldol coupling.

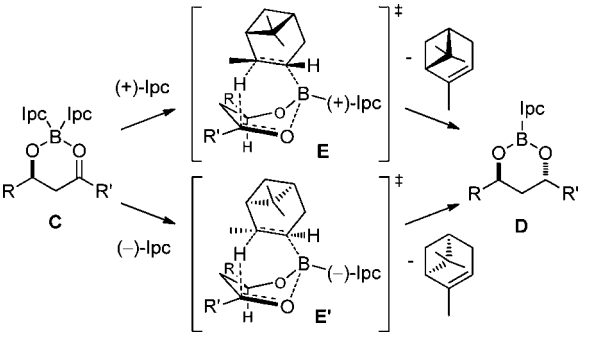
(16) (a) Roush, W. R. *J. Org. Chem.* **1991**, *56*, 4151. (b) Reetz, M. T. *Acc. Chem. Res.* **1993**, *26*, 462. (c) Evans, D. A.; Dart, M. J.; Duffy, J. L.; Yang, M. G. *J. Am. Chem. Soc.* **1996**, *118*, 4322.

β-substituent of the aldehyde was observed (viz. entries 5 and 7 as well as 6 and 8), with a Bn-group exerting a much stronger influence as compared to a TBS group. Only moderate selectivities were observed in nonmatched cases (entries 2, 6, 10) or in examples where the selectivity is exclusively derived from the Ipc-ligand (entry 11), again in full agreement with previous examples.[6c]

Importantly, in all cases 1,3-*anti* diol products were obtained with very high selectivities [*dr* (anti/syn) > 19:1], independently of the Ipc-isomer used. To unambiguously exclude any substrate control or coordinating effects in the reduction step, we investigated the coupling of benzaldehyde and acetone, which resulted again in the exclusive formation of 1,3-*anti* diol **18** (entry 11).[17] This allows the confident conclusion that the selectivity of the reduction step is independent of the nature of Ipc as well as substrate control.

Presumably, the high stereoselectivity observed in the reduction step may only be explained by a closed transition state with an intramolecular hydride transfer, in agreement with lower asymmetric inductions previously observed in intermolecular Ipc-mediated reductions.[7] Based on the accepted mechanism,[7c] an Ipc-induced transfer hydrogenation to the carbonyl group under extrusion of α-pinene would also be expected for the domino sequence developed herein, which was confirmed by identification of α-pinene in the NMR of the crude product. In agreement with the proposed transition state for Ipc-mediated aldol couplings,[18] a six-membered twist-boat-like transition state may also be proposed for the reduction step. As shown in Scheme 3, the reduction may be directed by the twist geometry of the six-membered borate **E**, which explains the observed 1,3-*anti* selectivity of this process.[19] This type of transition state is also in agreement with the lack of stereochemical influence of the Ipc-ligand observed in this domino reaction, as both isomers would proceed through closely related transition states (i.e., **E** and **E′**), leading to the same cyclic boronate **D**.

Scheme 3. Mechanistic Proposal for the 1,3-*anti* Reduction Process



In conclusion, we have developed a novel domino process for the highly diastereoselective synthesis of 1,3-*anti* diols from simple starting materials. Mechanistically, the procedure is based on a sequential Ipc-mediated aldol coupling/reduction sequence. It generates two new stereogenic centers in a highly concise fashion with excellent *anti*-selectivity and may be readily used for polyketide synthesis. It is expected that this cascade reaction will be efficiently applied in diverse syntheses of polyketides and polyfunctional substrates with 1,3-diol motifs.

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Supporting Information Available. Experimental details, spectral data, and copies of NMR spectra for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.

(17) Acetti, D.; Brenna, E.; Fuganti, C.; Gatti, F. G.; Serra, S. *Eur. J. Org. Chem.* **2010**, 142.

(18) (a) Hoffmann, R. W.; Ditrich, K.; Froech, S.; Cremer, D. *Tetrahedron* **1985**, *41*, 5517. (b) Li, Y.; Paddon-Row, M. N.; Houk, K. N. *J. Am. Chem. Soc.* **1988**, *110*, 3684. (c) Paterson, I.; Goodman, J. M. *Tetrahedron Lett.* **1989**, *30*, 997.

(19) Notably, an intermolecular reduction of chelated β-hydroxy ketones results in 1,3-*syn* product formation via a chairlike or half chairlike transition state. The proposed transition state for a 1,3-*anti* reduction requires using the Evans−Carreira protocol, which requires acidic conditions and proceeds via a hydride transfer within the six-membered chairlike transition state, which would not be possible for our system. See ref 3.