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Building Higher Carbohydrates via Dioxanone Aldol Chemistry: The α,α′-Bisaldol Approach

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A synthetic approach to higher carbohydrates via the sequence of two aldol reactions that proceed at the α and α′ positions of 2,2-dimethyl-1,3-dioxan-5-one (dioxanone) is described. As reported before, the first aldol reaction works well under organocatalytic conditions (proline catalysis), this is followed by protection of the hydroxy, deprotonation of the resulting compound using excess of LDA, and the second aldol addition. This sequence of reactions gives compounds having a straight-chain carbon skeleton with an oxygen-based functional group at each carbon. Most of the groups are protected. The utility of this strategy is illustrated by short syntheses of 6-*C*-phenyl-D-*glycero*-D-*allo*-hexopyranose and D-*erythro*-D-allooctopyranose

Introduction

Carbohydrates having a carbon backbone that is longer than six carbon atoms ("higher monosaccharides" or "higher-carbon sugars") have attracted much attention recently due to their interesting biological properties. Examples include higher aldoses that occur as chiral fragments in antibiotics, e.g., hikosamine (C_{11}) and lincosamine (C_8), and ketose-derived sialic acids such as KDO (C_8) and KDN (C_9). Even a brief review of relevant chemistry is beyond the scope of this communication (which focuses on dioxanone-based synthesis); interested readers are directed to recent reviews on the subject of synthesis of higher-carbon sugars;[1a–1d] it should also be noted that two thematic issues of *Chemical Reviews* are devoted to carbohydrate chemistry and glycobiology.[1e,1f] Briefly, most of the approaches to higher monosaccharides involve simple aldoses as the starting materials and either homologation by adding one-, two- or three-carbon fragments, or coupling of carbohydrate-derived building blocks as synthetic strategies, but some "totally synthetic" routes were described as well.[2] Due to their biological importance sialic acids have been studied extensively from different vantage points, including biological studies, modeling, design of non-natural analogs and stereoselective synthesis.[1b,1g–1k]

In the context of carbohydrate synthesis we are interested in exploring the use of 2,2-dialkyl-1,3-dioxan-5-ones as attractive scaffolds for ketoses and other poly-oxygenated compounds.[3] A number of research groups have published in this area, especially since it was discovered that dioxanones are good substrates for organocatalytic aldol reactions,[4] and the relevant chemistry has been reviewed from two different points of view.[5] The work of Enders' group involving SAMP/RAMP derivatives of dioxanones is especially noteworthy.[5a,6] However, the sequential aldol-aldol approach to the synthesis of carbohydrate derivatives from dioxanones has not been fully realized as yet, despite the fact that some preliminary observations pertaining to such reactions in the dioxanone system were published a few years ago.[3c,7] Below, we describe our recent studies on development of the dioxanone bisaldol methodology via a sequence of two aldol reactions – the first catalyzed by proline and the second proceeding via the corresponding lithium enolate and we highlight examples of stereocontrolled synthesis of higher sugars and their derivatives.

Results and Discussion

Our synthetic approach is shown in Scheme 1. The symmetrical dioxanone starting material (C_S or C_{2v}) was used as the substrate in the aldol reaction with a suitably chosen aldehyde. This first aldol reaction could give up to sixteen stereoisomers (relative stereochemistry being syn or *anti* and *cis* or *trans* with respect to each stereogenic element in the structure, if $R^1 = R^2$ the number of possible stereoisomers decreases to eight) but it had been established before that the selectivity of the reaction (both enantio- and diastereoselectivity) could be efficiently controlled to give either enantiomer of the *anti* mono-aldol by means of the enantioselecitve deprotonation methodology,[3] by the chiral auxiliary method,[6,7] or by organocatalysis with proline.[4] The challenge was in developing conditions for the second

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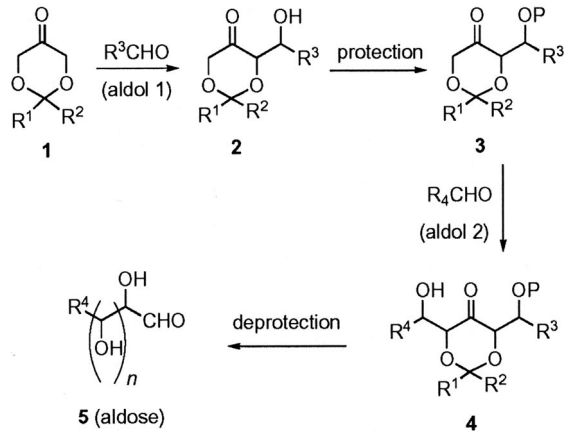
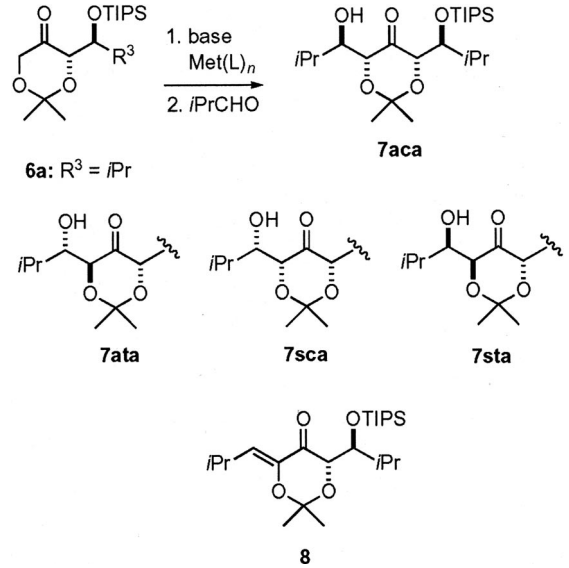
aldol reaction that should proceed in a reasonably high yield and diastereoselectivity to give the corresponding bisaldol.



Scheme 1. Synthetic strategy towards higher aldoses.

The bisaldol moiety (i.e., the β,β′-dihydroxycarbonyl fragment) occurs in natural products, such as epothilones and myriaporones,[8] and a number of synthetic approaches to compounds containing such juxtaposition of functional groups were reported.[8,9] We first investigated different conditions in the aldol addition reaction of trisisopropylsilyl (TIPS) protected pure *anti* isomer of the mono-aldol **6a** (Scheme 2, Table 1).



Scheme 2. The second aldol reaction.

A number of attempts to run the reaction under organocatalytic conditions failed (Table 1, Entry 1). This was, perhaps, not surprising, because if the second aldol addition was facile one would expect double aldol products to manifest themselves in "normal" proline catalytic cycles and this has been rarely observed.[10] Reactions involving titanium enolate or magnesium enolate of compound **6a** afforded only small amounts of dehydrated double aldol **8**. Experiments involving boron enolates (Entry 3) gave, as reported

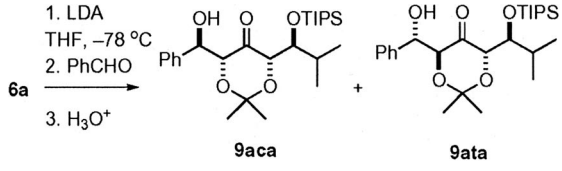
Table 1. Aldol addition reaction of dioxanone derivative **6a** to isobutyraldehyde (Scheme 2).

Entry	Conditions	Products	Yield (%)[a]
1	Proline,[b] DMSO, 5 °C	–	–
2	$TiCl_4$,[c] $(iPr)_2EtN$	**8** only	24
3	Chx_2BCl,[d] Et_3N, –78 °C	**7aca/7ata/(7sca + 7sta)** 13:86:1	96
4	MgI_2,[e] $(iPr)_2EtN$	**8** only	15
5	LDA[f]	**7aca/7ata/(7sca + 7sta)** 65:35:0	74

[a] Combined yield of all isolated products. [b] For details on organocatalytic conditions cf. ref.[4e] [c] Conditions: cf. ref.[9d] [d] Conditions: cf. ref.[3c] [e] Method description ref.[11] [f] For detailed conditions see the following section.

before,[3,7] predominantly the *anti-trans-anti* isomer of the double aldol product **7ata** with good selectivity and in good yield (note that only two of the four possible aldols were observed within NMR detection limit). However, boron enolates did not work well with aldehyde building blocks that contained sulfur moieties and this limitation rendered the boron enolate method poorly suited to our synthetic objectives (vide infra).

We then turned our attention to lithium enolates, the "tried and true" intermediates in aldol chemistry.[12] Initial attempts did not look promising, but after some experimentation we have established that the reaction works well if an excess of the base and an excess of the aldehyde are used (Scheme 3, Table 2). The first equivalent of the base presumably complexes to Lewis basic sites in the substrate and does not participate in deprotonation, upon addition of the aldehyde the first molar equivalent of the aldehyde is consumed in the addition reaction with LDA, which is a well known process.[13]



Scheme 3. The second aldol reaction via lithium enolate.

Table 2. Aldol reaction of lithium enolate of **6a** with benzaldehyde (Scheme 3).

Entry	Equiv. LDA	Equiv. PhCHO	Yield (%)	**9aca/9ata**
1	1.1	1	9	2.7:1
2	2.2	1	14	1.9:1
3	3.3	1	10	1.8:1
4	1.1	3	–	–
5	2.2	3	> 90	8:1
6	3.3	3	> 90	7.3:1

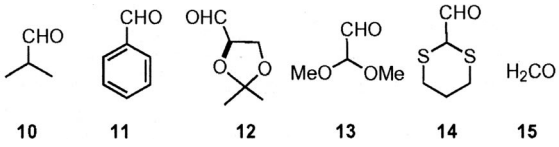
Having elaborated the conditions for the second aldol reaction via lithium enolates we then investigated a number of sequential processes where the first aldol reaction was done under organocatalytic conditions (proline, DMSO,

5 °C, 1–4 d), the product was purified and protected as the corresponding TIPS ether (one pure isomer), and was then subjected to enolization with LDA (2–3 equiv., THF, –78 °C), followed by addition of the second aldehyde. The results are summarized in Table 3.

Table 3. Bisaldol reactions of dioxanone **1** (R^1 = R^2 = Me) with aldehydes **10**–**15**.

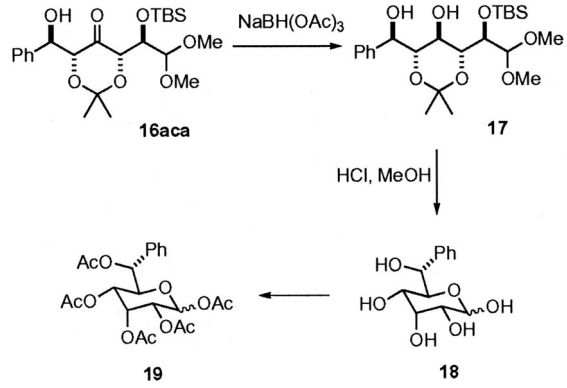
Entry	R^3CHO	R^4CHO	Products aca/ata/(sca + sta)	Yield (%)[a]
1	**10**	**10**	63:37:0	56 (68)
2	**10**	**11**	80:11:9	99
3	**10**	**14**	86:13:1	68 (74)
4	**11**	**14**	63:34:3	53
5	**13**	**10**	64:27:9	54
6	**13**	**14**	91:9:0	86 (97)
7	**13**	**12**	78:22:0	45 (79)
8	**13**	**11**	64:34:2	75
9	**13**	**15**	70:30:0	39 (40)
10	**12**	**12**	98:2:0	83 (99)

[a] Combined yield. Values in brackets refer to yields calculated on the basis of the recovered starting material (BORSM).



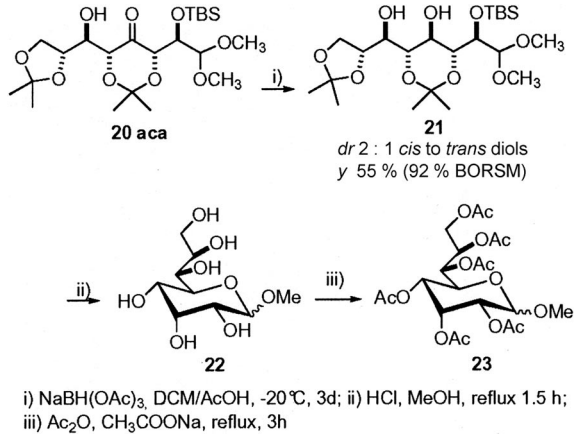
During this study we paid special attention to aldehydes that are useful building blocks for carbohydrate synthesis: monoprotected glyoxal derivatives **13** and **14** and protected glyceraldehyde **12**. While some systems clearly worked better than others, the following points should be noted: (i) in the best systems (Entries 2, 6 and 7) the aldol addition reactions proceeded in high yield, reasonable selectivity (the major products *anti-cis-anti* were obtained as pure compounds after chromatography). While the level of diastereoselectivity needs to be improved, the simplicity of this approach compensates for less than ideal distribution of isomeric products. The reaction with formaldehyde is noteworthy (Entry 9). In our studies with dioxanones we had never been able to accomplish a reaction with formaldehyde, despite trying a number of different conditions including organocatalysis. However, this reaction does proceed as the second aldol addition, albeit in low yield. It should be noted that a number of isolated aldol *anti-cis-anti* products comprise the complete carbon skeleton of carbohydrates and have the necessary oxygen functional groups in the right positions. Thus, easy to envisage functional group manipulations of these compounds (reduction-deprotection sequences) offer access to hexoses or their C-6 derivatives (Entries 3–5, 8–9), heptoses (Entry 6), octoses (Entry 7) and nonoses (Entry 10). We highlight selected conversions of these bisaldol products to the corresponding carbohydrates below.

Synthesis of 6-*C*-Phenyl-D-*glycero*-D-*allo*-hexopyranose: Derivatives of simple aldohexoses having an alkyl or aryl group connected to C-6 are important biologically active compounds.[14] The bisaldol strategy offers a quick access to these modified carbohydrates as shown in Scheme 4. The *anti-cis-anti* compound **16aca** was obtained as described in the preceding section and isolated in 50% yield. Reduction with sodium tris(acetoxy)borohydride[4b,15] gave the corresponding diol in 83% yield and 30:1 diastereoisomeric ratio (*dr*). Deprotection of the three hydroxy groups and the formyl group proceeded smoothly in "one pot" upon treatment with HCl affording the carbohydrate **18**, that was characterized as the acetate derivative, 6-*C*-phenyl-D-*glycero*-D-allohexopyranose pentaacetate **19** (25% yield).



Scheme 4. Synthesis of 6-*C*-phenyl-D-*glycero*-D-allohexopyranose.

D-*erythro*-D-Allooctopyranose: Compound **20aca** was isolated in 74% yield and was reduced to the corresponding diol **21** (57% yield). The aldooctose was then deprotected and characterized as the acetate derivative **23** (23% yield) Scheme 5.



Scheme 5. Synthesis of a D-*erythro*-D-allopyranose derivative.

Conclusions

In summary the two sequential aldol reactions on the dioxanone scaffold, the first catalyzed by proline and the second involving the lithium enolate of the protected first aldol product, proceeded stereoselectively and formed a

cornerstone of the synthetic strategy towards diastero- and enantioselective synthesis of higher carbohydrates. In this system proline organocatalysis and the lithium enolate methodology are complementing each other. We are working on expanding this methodology to allow access to more carbohydrate stereoisomers at higher levels of selectivity.

Experimental Section

Second Aldol Reaction. Typical Procedure

4-(1′-*tert*-Butyldimethylsilyloxy-2′,2′-dimethoxy)ethyl-6-[hydroxy-(phenyl)]methyl-2,2-dimethyl-1,3-dioxan-5-one (16aca): *n*BuLi (0.37 mL, 0.88 mmol, 2.38 M solution in hexanes) was added dropwise to a stirred solution of diisopropylamine (0.18 mL, 0.96 mmol, 2.4 equiv.) in THF (10 mL) at 0 °C under nitrogen. After 30 min the mixture was cooled to –78 °C and a solution of the TBS-protected aldol substrate (139 mg, 0.40 mmol, 1.00 equiv.) in THF was added slowly. The mixture was stirred for 40 min at –78 °C. PhCHO (110 mg, 0.11 mL, 1.00 mmol, 2.5 equiv.) was then added. After 20 min the reaction was quenched with concentrated phosphate buffer (pH 7.5; 10 mL) and extracted three times with diethyl ether. The combined organic layers were rinsed with saturated NaCl, dried with $MgSO_4$, concentrated, and fractionated by FCC (3–7% ethyl acetate in hexane) to give **16ata** (44.5 mg, 0.10 mmol, 25%) as a pale yellow liquid, and **16aca** (89.7 mg, 0.30 mmol, 50%) as a pale yellow liquid. Diastereoselectivity of the reaction was measured on the crude product by integration of peaks in ^{1}H NMR: δ = 5.12 (dd, J = 4.6 Hz), 4.89 (d, J = 8.4 Hz) 4.78 ppm (d, J = 8.4 Hz) and was found to be 2:64:34 *syn*/**aca**/**ata**.

16aca: $[\alpha]_D^{22}$ = +17 (c = 1.5, $CHCl_3$). IR: $\tilde{\nu}$ = 3535, 1737 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.42–7.24 (m, 5 H), 4.89 (d, J = 8.4 Hz, 1 H), 4.59 (d, J = 7.5 Hz, 1 H), 4.44 (dd, J_1 = 1.2, J_2 = 1.8 Hz, 1 H), 4.15 (dd, J_1 = 1.2, J_2 = 8.4 Hz, 1 H), 4.12 (dd, J_1 = 1.9, J_2 = 7.5 Hz, 1 H), 4.06 (br. s, 1 H), 3.46 (s, 3 H), 3.45 (s, 3 H), 1.41 (s, 3 H), 1.38 (s, 3 H) 0.90 (s, 9 H), 0.15 (s, 3 H), 0.11 (s, 3 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 208.97, 139.8, 128.1, 128.0, 127.6, 105.7, 98.7, 79.8, 79.1, 74.7, 73.7, 56.2, 56.0, 28.8, 26.1, 26.0, 20.6, 18.4, –4.2, –4.4 ppm. HRMS *m*/*z* calcd. for $C_{23}H_{38}O_7Si$ 472.2731 [M + NH_4], found 472.2729 (CI).

16ata: $[\alpha]_D^{29}$ = –64 (c = 1.85, $CHCl_3$). IR: $\tilde{\nu}$ = 3535, 1737 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.41–7.24 (m, 5 H), 4.78 (dd, J_1 = 1.7, J_2 = 8.4 Hz, 1 H), 4.52 (d, J = 7.5 Hz, 1 H), 4.31 (dd, J_1 = 1.2, J_2 = 1.7 Hz, 1 H), 4.15 (dd, J_1 = 1.2, J_2 = 8.4 Hz, 1 H), 4.09 (dd, J_1 = 1.7, J_2 = 7.5 Hz, 1 H), 3.63 (d, J = 1.7 Hz, 1 H), 3.45 (s, 3 H), 3.37 (s, 3 H), 1.32 (s, 3 H), 1.17 (s, 3 H), 0.88 (s, 9 H), 0.1 (s, 3 H), 0.09 (s, 3 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 209.3,139.9, 128.2, 128.0, 127.2, 105.4, 101.7, 77.9, 75.1, 73.8, 72.4, 56.5, 55.5, 26.2, 26.0, 24.0, 23.5, 18.3, –4.3, –4.7 ppm. HRMS *m*/*z* calcd. for $C_{23}H_{38}O_7Si$ 472.2731 [M + NH_4], found 472.2731 (CI).

Supporting Information (see also the footnote on the first page of this article): Procedures and spectroscopic data for for bis-aldols and carbohydrate derivatives.

Acknowledgments

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[1] Reviews: a) S. Jarosz, *J. Carbohydr. Chem.* **2001**, *20*, 93; b) I. Hemeon, A. J. Bennet, *Synthesis* **2007**, 1899; c) G. Casiraghi, G. Rassu, *Stud. Nat. Prod. Chem.* **1992**, *11*, 429; d) S. Jarosz, A. Zamojski, *Curr. Org. Chem.* **2003**, *7*, 13; e) R. A. Dwek, T. D. Butters, *Chem. Rev.* **2002**, *102*, 283; f) J. K. Bashkin, *Chem. Rev.* **2000**, *100*, 4265; g) S. Han, B. E. Collins, J. C. Paulson, *ACS Symp. Ser.* **2007**, *960*, 2; h) J. P. Kamerling, G. J. Gerwig, *Methods Mol. Biol.* **2006**, *347*, 69; i) D. K. Ress, R. J. Linhardt, *Curr. Org. Synth.* **2004**, *1*, 31; j) K. Ikeda, M. Sato, Y. Torisawa, *Curr. Med. Chem.: Anti-Infect. Agents* **2004**, *3*, 339; k) H. Ando, A. Imamura, *Trends Glycosci. Glycotechnol.* **2004**, *16*, 293.

[2] Recent examples: a) S. Jarosz, A. Gajewska, *Pol. J. Chem.* **2007**, *81*, 1949; b) A. Fuerstner, M. Wuchrer, *Chem. Eur. J.* **2006**, *12*, 76; c) H.-M. Liu, D.-P. Zou, E. Zhang, W.-G. Zhu, T. Peng, *Eur. J. Org. Chem.* **2004**, 2103; d) S. Jarosz, *Carbohydr. Res.* **2003**, *338*, 407; e) M. Jorgensen, E. H. Iversen, R. Madsen, *J. Org. Chem.* **2001**, *66*, 4625; f) J. Marco-Contellas, E. de Opazo, N. Arroyo, *Tetrahedron* **2001**, *57*, 4729; g) P. Vogel, *Curr. Org. Chem.* **2000**, *4*, 455; h) H. M. Liu, F.-W. Liu, X.-P. Song, J.-y. Zhang, Y. Lin, *Tetrahedron: Asymmetry* **2006**, *17*, 3230; i) C. DeMeo, U. Priyadarshani, *Carbohydr. Res.* **2008**, *343*, 1540.

[3] a) M. Majewski, D. M. Gleave, P. Nowak, *Can. J. Chem.* **1995**, *73*, 1616; b) M. Majewski, P. Nowak, *Synlett* **1999**, 1447; c) M. Majewski, P. Nowak, *J. Org. Chem.* **2000**, *65*, 5152; d) M. Majewski, R. Lazny, P. Nowak, *Tetrahedron Lett.* **1995**, *36*, 5465; e) N. Palyam, I. Niewczas, M. Majewski, *Tetrahedron Lett.* **2007**, *48*, 9195.

[4] a) D. Enders, T. Gasperi, *Chem. Commun.* **2007**, 88; b) C. Grondal, D. Enders, *Adv. Synth. Catal.* **2007**, *349*, 694; c) C. Grondal, D. Enders, *Tetrahedron* **2006**, *62*, 329; d) J. T. Suri, S. Mitsumori, K. Alberthofer, F. Tanaka, C. F. Barbas III, *J. Org. Chem.* **2006**, *71*, 3822; e) M. Majewski, I. Niewczas, N. Palyam, *Synlett* **2006**, *15*, 2387; f) D. Enders, S. Chow, *Eur. J. Org. Chem.* **2006**, 4578; g) C. Grondal, D. Enders, *Synlett* **2006**, 3507; h) I. Ibrahem, W. Zou, Y. Xu, A. Cordova, *Adv. Synth. Catal.* **2006**, *348*, 211; i) D. Enders, C. Grondal, *Angew. Chem. Int. Ed.* **2005**, *44*, 1210; j) I. Ibrahem, A. Cordova, *Tetrahedron Lett.* **2005**, *46*, 3363; k) J. T. Suri, D. B. Ramachary, C. F. Barbas III, *Org. Lett.* **2005**, *7*, 1383; l) J. Casas, M. Engqvist, I. Ibrahem, B. Kaynak, A. Cordova, *Angew. Chem. Int. Ed.* **2005**, *117*, 1367.

[5] a) D. Enders, M. Voith, A. Lenzen, *Angew. Chem. Int. Ed.* **2005**, *44*, 1304; b) M. Markert, R. Mahrwald, *Chem. Eur. J.* **2008**, *14*, 40.

[6] a) D. Enders, B. Bockstiegel, *Synthesis* **1989**, 493; b) D. Enders, J. Barbion, *Chem. Eur. J.* **2008**, *14*, 2842, and references cited therein.

[7] a) D. Enders, S. J. Ince, *Synthesis* **2002**, 619; b) D. Enders, G. Raabe, S. J. Ince, S. M. Bonnekessel, J. Runsink, *Synlett* **2002**, 962.

[8] a) M. Kalesse, E. Claus, A. Pahl, P. G. Jones, H. M. Meyer, *Tetrahedron Lett.* **1997**, *38*, 1359; b) K. Biswas, H. Lin, J. T. Njardarson, M. D. Chappell, T.-C. Chou, Y. Guan, W. P. Tong, L. He, S. B. Horwitz, S. J. Danishefsky, *J. Am. Chem. Soc.* **2002**, *124*, 9825; c) K. N. Fleming, R. E. Taylor, *Angew. Chem. Int. Ed.* **2004**, *43*, 1728.

[9] Examples: a) R. Annunziata, M. Cinquini, F. Cozzi, A. Restelli, *J. Chem. Soc., Chem. Commun.* **1984**, 1253; b) D. A. Evans, P. J. Coleman, B. Cote, *J. Org. Chem.* **1997**, *62*, 788; c) C. Delas, O. Blacque, C. Moise, *Tetrahedron Lett.* **2000**, *41*, 8269; d) D. E. Ward, G. E. Beye, M. Sales, I. Q. Alarcon, H. M. Gillis, V. Jheengut, *J. Org. Chem.* **2007**, *72*, 1667; e) G. P. Luke, J. Morris, *J. Org. Chem.* **1995**, *60*, 3013.

[10] a) D. Gryko, R. Lipinski, *Eur. J. Org. Chem.* **2006**, 3864; b) S. Luo, X. Mi, L. Zhang, S. Liu, H. Xu, J.-P. Cheng, *Tetrahedron* **2007**, *63*, 1923; c) K. Funabiki, H. Nagaya, M. Ishihara, M. Matsui, *Tetrahedron* **2006**, *62*, 5049; d) C. Ji, Y. Peng, C. Huang, N. Wang, Z. Luo, Y. Jiang, *J. Mol. Catal. A* **2006**, *246*, 136.

[11] H.-X. Wei, K. Li, Q. Zhang, R. L. Jasoni, J. Hu, P. W. Pare, *Helv. Chim. Acta* **2004**, *87*, 2354.
[12] a) R. Mahrwald (Eds.), *Modern Aldol Reactions*, vol. 1 and 2, Wiley-VCH, Weinheim, **2004**; b) D. Caine in *Science of Synthesis*, vol. 8a (Eds.: M. Majewski, V. Snieckus), Thieme, Stuttgart, **2006**; chapter 8.1.17.
[13] a) J. Green in *Science of Synthesis*, vol. 8a (Eds.: M. Majewski, V. Snieckus), Thieme, Stuttgart, **2006**; chapter 8.1.15; b) M. Majewski, D. M. Gleave, *J. Organomet. Chem.* **1994**, *470*, 1.
[14] Y. Bleriot, C. R. Veighey, K. H. Smelt, J. Cadefau, W. Stalmans, K. Biggadike, A. L. Lane, M. Mueller, D. J. Watkin, G. W. J. Fleet, *Tetrahedron: Asymmetry* **1996**, *7*, 2761.
[15] D. A. Evans, K. T. Chapman, E. M. Carreira, *J. Am. Chem. Soc.* **1988**, *110*, 3560.

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