Diastereo- and enantio-selective synthesis of 6-heterosubstituted-3,5-dihydroxyesters: novel precursors of mevinolin analogues

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The diastereoselective addition of 1,3-bis(trimethylsilyloxy)-1-methoxybutadiene 2 to readily available α-heterosubstituted aldehydes (*S*)-1 affords after *syn*-diastereoselective reduction HMG-CoA-reductase-inhibitor-precursors (*S,R,S*)-4 and 5 with various substitution patterns and high enantiomeric and diastereoisomeric excesses (ee = 93–>96%; de = 95–>96%) in good yields.

Owing to the importance of the 1,3-diol functionality as a key structural feature in pharmaceutically active compounds, such as HMG-CoA-reductase-(HMGR)-inhibitors[1] and macrolide antibiotics,[2] an increasing number of methodologies have dealt with their synthesis in a diastereo- and enantio-controlled manner.[3]

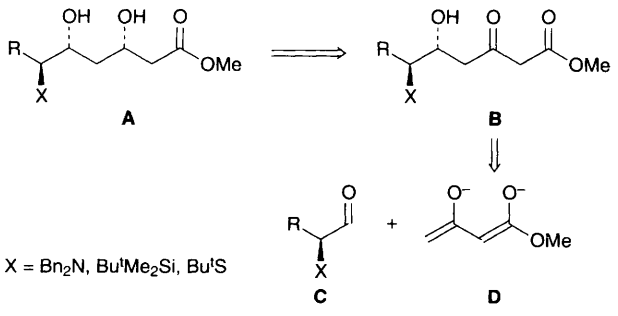
Our approach to the diastereo- and enantio-selective synthesis of 6-heterosubstituted *syn*-3,5-dihydroxy-esters **A**, representing the key structural feature of HMGR-inhibitors, is based on the diastereoselective 1,2-addition of acetoacetate d^4-reagents **D** to chiral α-heterosubstituted aldehydes **C** followed by *syn*-selective reduction of the resulting 5-hydroxy-3-oxoesters **B** (Scheme 1).

The chiral α-heterosubstituted aldehydes **C** were prepared in highly enantiomerically enriched form, following the procedure of Reetz *et al.*[4] [(*S*)-**1a–c**; X = NBn_2], or by application of the SAMP-/RAMP-hydrazone methodology [(*S*)-**1d–f**; X = Bu^tMe_2Si, Bu^tS], previously developed in our laboratories.‡[5] The ee's of the chiral aldehydes could be determined by formation of the Mosher esters[6] {(*S*)-MTPA-Cl [MTPA = α-methoxy-α-(trifluoromethyl)phenylacetic acid], DMAP, CH_2Cl_2, 2 h, 0 °C} after reduction to the corresponding alcohols [$NaBH_4$, CH_2Cl_2, 1 h, −78–0 °C]. Integration of the two methoxy-signals in the ^{1}H NMR spectrum indicated ee values of 93–>96% (Table 1).

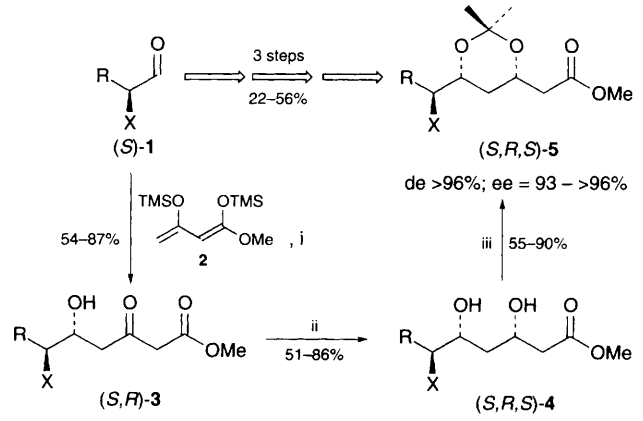
The subsequent optimisation of the aldol reaction conditions using several acetoacetate d^4-reagents resulted in the application of 1,3-bis(trimethylsilyloxy)-1-methoxybutadiene **2**,[7] which has so far found only limited applications in diastereoselective 1,2-additions to chiral α-substituted aldehydes.[8a–c] Thus, adding the corresponding aldehyde (*S*)-**1** and titanium tetrachloride to a vigorously stirred solution of **2** in dichloromethane furnished 6-heterosubstituted 5-hydroxy-3-oxoesters (*S,R*)-**3** as single diastereoisomers (Table 1) in moderate to good yields (54–87%).§ Finally, we reduced the keto group of the aldol products (*S,R*)-**3** diastereoselectively, using tri(butyl)-borane–pivalic acid–sodium borohydride in THF–MeOH,[9c] to afford the *syn*-diols (*S,R,S*)-**4** with complete stereocontrol (X = NBn_2, Bu^tMe_2Si) and fair to good yields (51–86%). However, in the case of X = Bu^tS only a 9:1 mixture of *syn*:*anti*-dihydroxyesters (*S,R,S*)-**4** could be obtained, as determined by ^{13}C NMR spectra analyses.¶ The relative configuration of the newly created stereogenic centres could be assigned by ^{1}H NMR NOE measurements after conversion to the 1,3-dioxanes (*S,R,S*)-**5** [2,2-dimethoxypropane–BF_3·OEt_2–CH_2Cl_2] followed by chromatographic purification or recrystallisation from pentane. Thus, we were also able to increase the de's of (*S,R,S*)-**5f,g** to 95% (Table 1).

The determination of the ee's of the 1,3-dioxanes (*S,R,S*)-**5** was carried out by ^{1}H NMR spectroscopy using the chiral cosolvent (−)-(*R*)-1-(9-anthryl)-2,2,2-trifluoroethanol and by comparison with the corresponding racemic compounds.‖ In conclusion, as is evident from the data given in Table 1, no racemisation occurred in the whole reaction sequence. The observed *anti*-selectivity of the Mukaiyama aldol reaction to chiral aldehydes (*S*)-**1**, not prone to chelation, is in complete agreement with similar Lewis acid promoted reactions of enol silanes[10] and can be rationalized by application of a Felkin–Anh transition state.[11]

In summary, the *anti*-selective nucleophilic 1,2-addition of methyl acetoacetate d^4-equivalent **2** to readily available highly enantiomerically enriched α-heterosubstituted aldehydes followed by *syn*-selective reduction of the keto group, as described here, offers an efficient entry to 6-heterosubstituted 3,5-dihydroxyesters in high de and ee.** Starting from the enantiomeric



Scheme 1 Retrosynthetic analysis of 6-heterosubstituted *syn*-3,5-dihydroxyesters **A**



Scheme 2 *Reagents and conditions*: i, **2** (3.0 equiv.), $TiCl_4$ (2.1 equiv.), CH_2Cl_2, −78 °C; ii, Bu_3B (1.2 equiv.), $C_4H_9CO_2H$ (0.1 equiv.), $NaBH_4$ (1.5 equiv.); iii, $MeC(OMe)_2Me$ (2–20 equiv.), BF_3·OEt_2 (1–20 equiv.), CH_2Cl_2, −78–0 °C

Table 1 Enantioselective synthesis of HMG-CoA-reductase-inhibitor precursors (*S,S,R*)-**5** *via* 1,2-addition of 1,3-*bis*-(trimethylsilyloxy)- butadiene **2** to chiral α-heterosubstituted aldehydes (*S*)-**1** followed by *syn*-stereoselective reduction of the keto group of (*S,R*)-**3** to (*S,R,S*)-**4**

Starting material	R	X	ee[a] [(*S*)-**1**] (%)	Yield **1** → **3** (%)	Yield **3** → **4** (%)	Yield **4** → **5** (%)	de[b] (%)	ee[c] **5** (%)	$[\alpha]_D^{RT}$ **5** (*c*, CH_2Cl_2)
(*S*)-**1a**	Pr^i	NBn_2	>96	60	67	55	>96	>96	−40.6 (0.93)
(*S*)-**1b**	Bu^t	NBn_2	>96	71	51	68	>96	>96	−43.4 (0.84)
(*S*)-**1c**	Bn	NBn_2	>96	71	61	81	>96	>96	−25.9 (0.73)
(*S*)-**1d**	Bn	Bu^{t}Me$_2$Si	93	54	55	90	>96	93	+34.3 (0.79)
(*S*)-**1e**	DCBn[d]	Bu^{t}Me$_2$Si	95	60	52	90	>96	95	+36.5 (0.76)
(*S*)-**1f**	Bn	Bu^{t}S	93	87	78	83	95[e]	93	+15.5 (0.52)
(*S*)-**1g**	DCBn[d]	Bu^{t}S	94	81	86	67	95[e]	94	+8.8 (0.72)

[a] Determined after conversion into the corresponding MTPA-esters followed by ^{1}H NMR analysis (Varian 300 MHz spectrometer). [b] Determined by ^{13}C NMR spectroscopy after column chromatography. [c] Determined by ^{1}H NMR spectroscopy using (−)-(*R*)-1-(9-anthryl)-2,2,2-trifluoro- ethanol as chiral cosolvent (Varian 300 MHz spectrometer). [d] DCBn: 2,4-dichlorobenzyl. [e] After recrystallisation from pentane.

aldehydes (*R*)-**1** (X = R_3Si, RS), accessible from the corresponding RAMP-hydrazones, the asymmetric synthesis of potential HMGR-inhibitor precursors is possible. This project is under current investigation in our laboratories.

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Footnotes

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‡ New chiral aldehydes (*S*)-**1e,g** were fully characterized by ^{1}H NMR, ^{13}C NMR, IR, MS and elemental analyses.

§ Refs 8*a,b* emphasize the importance of precomplexation of the chiral aldehyde to the Lewis acid to gain high diastereoselectivities. However, following the inverse addition procedure, as described here, we obtained the same selectivities and superior chemical yields.

¶ Attempted optimisation of the reaction conditions (trialkyl- and alkoxydialkyl-boranes, solvent, temperature, time) proved fruitless with no improvement of the stereoselectivity of the *syn*-reduction. The reason for the difference in behaviour of (*S,R*)-**3f,g** remains unclear.

‖ Racemic compounds **5** were prepared in the same manner previously described starting with racemic aldehydes **1**.

** All new compounds gave correct analytical data (^{1}H NMR, ^{13}C NMR, IR, MS and elemental analyses or HRMS).

References

1 Review: T. Rosen and C. H. Heathcock, *Tetrahedron*, 1986, **42**, 4909; T. Hiyama, G. B. Reddy, T. Minami, T. Hanamato, *Bull. Chem. Soc. Jpn.*, 1995, **68**, 350 and references cited therein.

2 For a review see: T. Oishi and N. Nakata, *Synthesis*, 1990, 635.

3 For representative examples see: S. Nagashima, T. Taishi and K. Kanematsu, *Tetrahedron Lett.*, 1994, **35**, 3577; M. S. Ermolenko, A. Olesker and G. Lukacs, *Tetrahedron Lett.*, 1994, **35**, 715 and references cited therein; B. Henkel, A. Kunath and H. Schick, *Tetrahedron: Asymmetry*, 1994, **5**, 17 and references cited therein; M. Scialdone and C. R. Johnson, *Tetrahedron Lett.*, 1995, **36**, 43; H. J. M. Gijsen and C.-H. Wong, *J. Am. Chem. Soc.*, 1994, **116**, 8422; M. H. Ansari, T. Kusumoto and T. Hiyama, *Tetrahedron Lett.*, 1993, **34**, 8271; T. Hiyama, T. Minami and K. Takahashi, *Bull. Chem. Soc. Jpn.*, 1995, **68**, 364 and reference cited therein; G. Beck, H. Jendralla and K. Kesseler, *Synthesis*, 1995, 1014 and references cited therein; A. Kumar and D. C. Dittmer, *J. Org. Chem.*, 1994, **59**, 4760 and references cited therein; G. E. Keck and D. Krishnamurthy, *J. Am. Chem. Soc.*, 1995, **117**, 2363; E. M. Carreira, R. A. Singer and W. Lee, *J. Am. Chem. Soc.*, 1994, **116**, 8837; M. Hayashi, T. Inoue, Y. Miyamoto and N. Oguni, *Tetrahedron*, 1994, **50**, 4385.

4 M. T. Reetz, M. W. Drewes and A. Schmitz, *Angew. Chem., Int. Ed. Engl.*, 1987, **99**, 1141.

5 D. Enders, B. B. Lohray, F. Burkamp, V. Bushan and R. Hett, *Liebigs Ann. Chem.*, in the press; D. Enders, T. Schäfer, O. Piva and A. Zamponi, *Tetrahedron*, 1994, **51**, 3349.

6 J. A. Dale, D. L. Dull and H. S. Mosher, *J. Org. Chem.*, 1969, **34**, 2543.

7 K. Yamamoto, S. Suzuki and J. Tsuji, *Chem. Lett.*, 1978, 649.

8 (*a*) D. A. Evans and W. C. Black, *J. Am. Chem. Soc.*, 1993, **115**, 4497; (*b*) H. Hagiwara, K. Kimura and H. Uda, *J. Chem. Soc., Perkin Trans 1*, 1992, 693; (*c*) S. Hashiguchi, A. Kawada and H. Natsugari, *J. Chem. Soc., Perkin Trans 1*, 1991, 2435.

9 (*a*) C. A. Sarko, I. C. Guch and M. DiMare, *J. Org. Chem.*, 1994, **59**, 705 and references cited therein; (*b*) K. Narasaka and F.-C. Pai, *Tetrahedron*, 1984, **40**, 2233; (*c*) M. Sletzinger, T. R. Verhoeven, R. P. Volante, J. M. McNamara, E. G. Corley and T. M. H. Liu, *Tetrahedron Lett.*, 1985, **26**, 2951.

10 K. Mikami, M. Terada and T. Nakai, *J. Chem. Soc., Chem. Commun.*, 1993, **4**, 343; M. T. Reetz, *Angew. Chem., Int. Ed. Engl.*, 1991, **30**, 1531; R. Annunziata, M. Cinquini, F. Cozzi, P. G. Cozzi and E. Consolandi, *J. Org. Chem.*, 1992, **57**, 456.

11 M. Cherest, H. Felkin and N. Prudent, *Tetrahedron Lett.*, 1968, 2199; N. T. Anh and O. Eisenstein, *Nouv. J. Chim.*, 1977, **1**, 61.

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