Pergamon

Tetrahedron Letters 43 (2002) 6145–6148

TETRAHEDRON LETTERS

Stereoselective synthesis of *syn*,*syn*-2-methyl-1,3-diols through one-pot aldol–reduction sequence

Marta Galobardes, Marisa Mena, Pedro Romea,* Fèlix Urpí* and Jaume Vilarrasa

Departament de Química Orgànica, Universitat de Barcelona, 08028 Barcelona, Catalonia, Spain

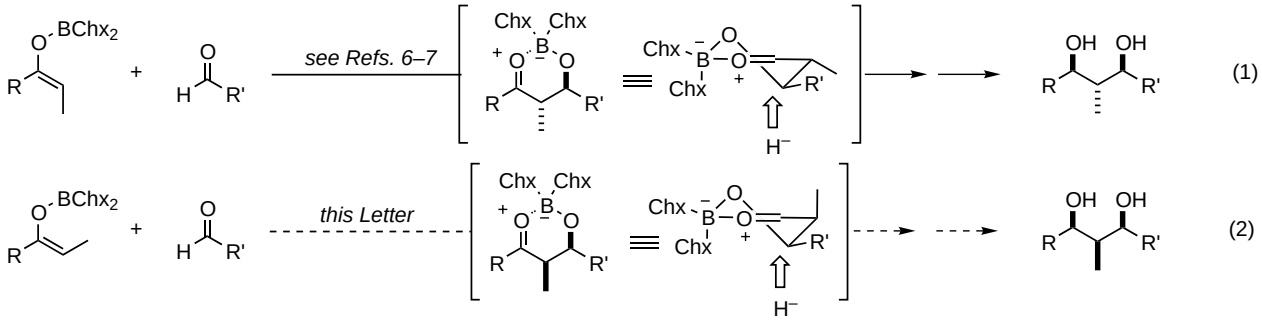
Received 17 June 2002; revised 1 July 2002; accepted 2 July 2002

Abstract—Chx_2BCl-mediated *syn*-aldol reaction of the α-OTBS lactate-derived ketone **1** followed by in situ reduction of the resulting boron aldolate with $LiBH_4$ lead to complete stereoselectivity for the boronates **2** in 80–95% yields. Then, a very mild oxidative work-up of **2** (H_2O_2/NaOAc in THF–H_2O) allows isolation of *syn*,*syn*-2-methyl-1,3-diols **3** in yields up to 95% without migration of the TBS group.

Stereoselective synthesis of acyclic 1,3-diols has attracted much attention since these units are embedded in the structure of a large array of polyketide natural products. In view of the easy availability of β-hydroxyketones, most of the strategies addressed to the synthesis of 1,3-diols rely on a two-step process: (i) stereoselective aldol reaction[1,2] and (ii) stereoselective reduction of the corresponding β-hydroxyketone.[3–5] A noteworthy exception is the boron mediated one-pot *anti* aldol–reduction sequence developed by Paterson[6,7] which, taking advantage of the structurally rigid boron aldolate intermediate, favours the addition of the hydride ion from an external source yielding the *anti*,*anti*-2-methyl-1,3-diols shown in Eq. (1) (see Scheme 1).[8]

We have recently disclosed that the Chx_2BCl-mediated aldol reaction of α-OTBS ketones[9] affords *syn* aldol adducts in excellent yields and diastereoselectivities up to 99:1.[10] Then, we envisioned that the boron aldolates involved in this reaction might be reduced in situ to afford the *syn*,*syn*-2-methyl-1,3-diols shown in Eq. (2) (see Scheme 1), which would improve the scope of the above-mentioned methodology.

In preliminary studies, we observed that aldol reaction of (*S*)-2-*tert*-butyldimethylsilyloxy-3-pentanone (**1**)[11] with benzaldehyde (**a**) followed by reduction ($LiBH_4$) of the resulting aldolate afforded a reaction mixture containing boronate **2a**. However, oxidative work-up under the reported conditions (H_2O_2 in MeOH/aqueous 2.5 M



Scheme 1.

Keywords: aldol reactions; asymmetric reactions; diols; stereocontrol.

* Corresponding authors. Fax: +34 93 339 78 78; e-mail: promea@qo.ub.es; furpi@qo.ub.es

0040-4039/02/$ - see front matter
PII: S0040-4039(02)01289-3

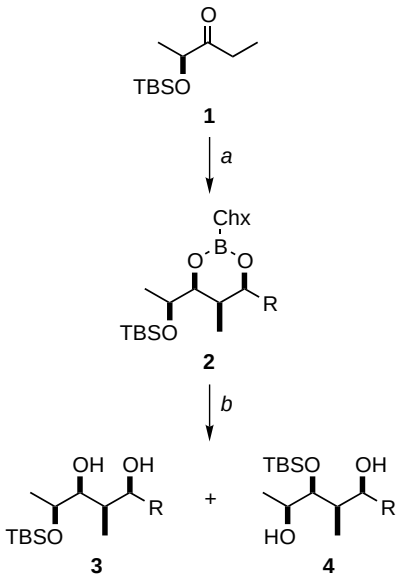
NaOH 1:1) afforded non-reproducible yields and, more disappointingly, a mixture (3:1 by ^{1}H NMR) of two inseparable diols, **3a** and **4a**.[12,13]

Given that the TBS protecting group is prone to migrate[14] under the basic conditions used along the overall process, we decided to carry out a careful analysis of the reaction sequence.

First of all, boronates **2** were prepared from ketone **1** and several aldehydes (**a**–**e**) and purified by chromatography.[15,16] The yields are summarised in Table 1. ^{1}H NMR (500 MHz) spectra of **2** showed the presence of just one diastereomer, which proves the high level of stereocontrol attained in the aldol–reduction sequence. Stereochemistry of boronates **2** depicted in Scheme 2 is based on the known stereochemical outcome of boron-mediated aldol reactions of ketone **1**[10] and of related reductions; ^{1}H NMR spectra also support these assignments.

Conversion of **2** into the desired 1,3-diols was then evaluated.

According to the reported procedure, it was expected 1,3-diols **3** to be obtained in good yields by treatment of **2** with H_2O_2 in MeOH/aqueous 2.5 M NaOH 1:1 (method A). In our case, these conditions produced the partial migration of the TBS group observed in preliminary experiments (see Scheme 2 and entries 1 and 8 in Table 2). Our efforts to overcome this problem did not afford good results: neither the use of neutral or buffered media nor replacement of NaOH by other bases allowed isolation of 1,3-diols **3** in acceptable yields. Given that poor solubility of **2** in MeOH/H_2O could be to some extent the reason of the aforementioned troubles, we considered the possibility of carrying out this oxidation with perborate in THF/H_2O 1.5:1 (method B).[7a,17] Again, the basicity of the reagent produced the undesired migration of the TBS group (see entries 2, 5, and 9 in Table 2). Eventually, it was found that very pure *syn* 1,3-diols **3** can be obtained by means of H_2O_2 in THF/H_2O 3:1 using 2 equiv. of NaOAc (method C).[18] The results are summarised in Table 2.



Scheme 2. *Reagents and conditions*: (a) i. Chx_2BCl, Et_3N, Et_2O; ii. RCHO; iii. Et_3N, $LiBH_4$. (b) See text and Table 2.

Having sorted out the problems involved in the sequence, it was worth trying to apply the optimal conditions in a synthetically more useful procedure which implies avoidance of the isolation of the boronate intermediate. Therefore, reaction mixtures obtained after the aldol–reduction process were treated with H_2O_2 and NaOAc in THF/H_2O. We were pleased to obtain the desired 1,3-diols **3** in excellent yields; however, their purification was often hampered by the presence of non-identified impurities which presumably

Table 1. Preparation of boronates **2**

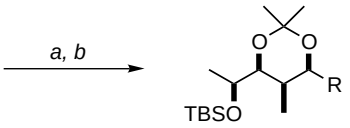
Entry	Aldehyde	R	Boronate	Yield (%)[a]
1	**a**	Ph	**2a**	90
2	**b**	(*E*) CH_3CH=CH	**2b**	80
3	**c**	H_2C=$C(CH_3)$	**2c**	90
4	**d**	$(CH_3)_2CHCH_2$	**2d**	87
5	**e**	$(CH_3)_2CH$	**2e**	95

[a] Isolated yield.

Table 2. Oxidation of boronates **2**

Entry	Boronate	Method[a]	Time (h)	**3**:**4**	Yield (%)[b]
1	**2a**	A	1	3:1	80
2		B	12	3:1	92
3		C	2	>95:5	95
4	**2b**	C	2	>95:5	92
5	**2c**	B	12	3:1	67
6		C	3.5	>95:5	86
7	**2d**	C	3.5	>95:5	90
8	**2e**	A	1	3:1	90
9		B	12	5.5:1	95
10		C	7.5	>95:5	89

[a] Method A: H_2O_2, MeOH/2.5 M aq. NaOH (1:1). Method B: $NaBO_3{\cdot}4H_2O$, THF/H_2O (1.5:1). Method C: H_2O_2, NaOAc, THF/H_2O (3:1).
[b] Isolated yield.



Scheme 3. *Reagents and conditions*: (a) See Refs. 16 and 18. (b) 2,2-Dimethoxypropane, CH_2Cl_2, PPTS cat.

Table 3. Protected 1,3-diols **5** from ketone **1**

Entry	Aldehyde	R	Yield (%)[a]
1	**a**	Ph	65
2	**c**	$H_2C{=}C(CH_3)$	71
3	**e**	$(CH_3)_2CH$	55

[a] Isolated overall yield.

arise from the reductive step. Then, protection of **3** as a cyclic acetal was undertaken in order to obtain pure products and, also, to get more evidences about the stereochemical outcome of the process through NMR studies (see Scheme 3). Enantiopure acetals **5** were finally obtained in 55–71% yield from **1** after chromatographic purification (see Table 3).[19]

In summary, the boron-mediated aldol reaction of the α-OTBS ketone **1** followed by in situ reduction with $LiBH_4$ proceeds with an excellent stereochemical control. Oxidative treatment of the resulting boronates **2** under very mild conditions avoids the migration of the TBS group and gives access to pure *syn*,*syn*-2-methyl-1,3-diols. Application of this methodology to the synthesis of natural products is currently in progress in our laboratories and will be reported in due course.

Acknowledgements

Financial support from the Ministerio de Educación y Cultura (DGESIC, Grant PM98-1272) and the Generalitat de Catalunya (1998SGR00040 and 2000SGR00021) and a doctorate studentship (Universitat de Barcelona) to M.G. are acknowledged.

References

1. For a review on stereoselective aldol reactions, see: Cowden, C. J.; Paterson, I. In *Organic Reactions*; Paquette, L. A., Ed.; John Wiley and Sons: New York, 1997; Vol. 51, pp. 1–200.
2. For recent developments on stereoselective catalytic aldol reactions, see: Carreira, E. M. In *Comprehensive Asymmetric Catalysis*; Jacobsen, E. N.; Pfaltz, A.; Yamamoto, H., Eds.; Springer: Heidelberg, 1999; Vol. 3, pp. 997–1065.
3. For a review on diastereoselective reduction of carbonyl groups, see: Davis, A. P. In *Stereoselective Synthesis, Methods of Organic Chemistry* (*Houben-Weyl*); Helmchen, G.; Hoffmann, R. W.; Mulzer, J.; Schaumann, E., Eds.; Thieme: Stuttgart, 1995; Vol. E21d, pp. 3988–4048.
4. For diastereoselective reductions of β-hydroxy ketones leading to *syn* 1,3-diols, see: (a) Narasaka, K.; Pai, F.-C. *Tetrahedron* **1984**, *40*, 2233–2238; (b) Kiyooka, S.-i.; Kuroda, H.; Shimasaki, Y. *Tetrahedron Lett*. **1986**, *27*, 3009–3012; (c) Chen, K.-M.; Hardtmann, G. E.; Prasad, K.; Repic, O.; Shapiro, M. J. *Tetrahedron Lett*. **1987**, *28*, 155–158; (d) Evans, D. A.; Hoveyda, A. H. *J. Org. Chem*. **1990**, *55*, 5190–5192; (e) Sarko, C. R.; Collibee, S. E.; Knorr, A. L.; DiMare, M. *J. Org. Chem*. **1996**, *61*, 868–873; (f) Bartoli, G.; Bellucci, M. C.; Bosco, M.; Dalpozzo, R.; Marcantoni, E.; Sambri, L. *Chem. Eur. J*. **2000**, *6*, 2590–2598.
5. For diastereoselective reductions of β-hydroxy ketones leading to *anti* 1,3-diols, see: (a) Evans, D. A.; Chapman, K. T.; Carreira, E. M. *J. Am. Chem. Soc*. **1988**, *110*, 3560–3578; (b) Evans, D. A.; Hoveyda, A. H. *J. Am. Chem. Soc*. **1990**, *112*, 6447–6449; (c) Keck, G. E.; Wager, C. A.; Sell, T.; Wager, T. T. *J. Org. Chem*. **1999**, *64*, 2172–2173.
6. (a) Paterson, I.; Perkins, M. V. *Tetrahedron Lett*. **1992**, *33*, 801–804; (b) Paterson, I.; Perkins, M. V. *Tetrahedron* **1996**, *52*, 1811–1834.
7. For recent applications, see: (a) Nicolaou, K. C.; Murphy, F.; Barluenga, S.; Ohshima, T.; Wei, H.; Xu, J.; Gray, D. L. F.; Baudoin, O. *J. Am. Chem. Soc*. **2000**, *122*, 3830–3838; (b) Perkins, M. V.; Sampson, R. A. *Org. Lett*. **2001**, *3*, 123–126; (c) Paterson, I.; Florence, G. J.; Gerlach, K.; Scott, J. P.; Sereinig, N. *J. Am. Chem. Soc*. **2001**, *123*, 9535–9544; (d) Paterson, I.; Chen, D. Y.-K.; Franklin, A. S. *Org. Lett*. **2002**, *4*, 391–394.
8. For other reports dealing with aldol–reduction sequences, see: (a) Bonini, C.; Rascioppi, R.; Righi, G.; Rossi, L. *Tetrahedron: Asymmetry* **1994**, *5*, 173–176; (b) Mahrwald, R.; Costisella, B. *Synthesis* **1996**, 1087–1089; (c) Bodnar, P. M.; Shaw, J. T.; Woerpel, K. A. *J. Org. Chem*. **1997**, *62*, 5674–5675; (d) Mahrwald, R.; Ziemer, B. *Tetrahedron* **1999**, *55*, 14005–14012; (e) Lu, L.; Chang, H.-Y.; Fang, J.-M. *J. Org. Chem*. **1999**, *64*, 843–853; (f) Mascarenhas, C. M.; Duffey, M. O.; Liu, S.-Y.; Morken, J. P. *Org. Lett*. **1999**, *1*, 1427–1429.
9. (a) Figueras, S.; Martín, R.; Romea, P.; Urpí, F.; Vilarrasa, J. *Tetrahedron Lett*. **1997**, *38*, 1637–1640; (b) Esteve, C.; Ferreró, M.; Romea, P.; Urpí, F.; Vilarrasa, J. *Tetrahedron Lett*. **1999**, *40*, 5079–5082.
10. Galobardes, M.; Gascón, M.; Mena, M.; Romea, P.; Urpí, F.; Vilarrasa, J. *Org. Lett*. **2000**, *2*, 2599–2602.
11. Ferreró, M.; Galobardes, M.; Martín, R.; Montes, T.; Romea, P.; Rovira, R.; Urpí, F.; Vilarrasa, J. *Synthesis* **2000**, 1608–1614.
12. Structure of **4a** is temptative. It has been assumed that migration of TBS group proceeds to the closest free OH.
13. Treatment of a 3:1 mixture of **3a** and **4a** with HF 48% -CH_3CN for 45 min under standard deprotection conditions affords a 86% of a single triol, which was identified as (1*R*,2*R*,3*S*,4*S*)-2-methyl-1-phenyl-1,3,4-pentanetriol.
14. Greene, T. W.; Wuts, P. G. M. *Protective Groups in Organic Synthesis*; John Wiley and Sons: New York, 1999.
15. All new compounds have spectroscopic and analytical data consistent with the assigned structure.

16. **General procedure**. To a cooled (−78°C) solution of **1** (108 mg, 0.5 mmol) in Et_2O (2 mL) was added dropwise Chx_2BCl (0.16 mL, 0.75 mmol) followed by Et_3N (0.14 mL, 1 mmol). The aldehyde (1 mmol) was added 2 h later and the reaction mixture was further stirred at −78°C for 3 h and kept at −20°C overnight. It was cooled at −78°C, Et_3N (0.14 mL, 1 mmol) was added, and few minutes later a 2 M $LiBH_4$ solution in THF (1.25 mL, 2.5 mmol). The reaction mixture was stirred at −78°C for 1.5 h and quenched with NH_4Cl sat (2.5 mL). Upon warming to rt the mixture was partitioned between NH_4Cl sat (5 mL) and Et_2O (3×15 mL). The organic extracts were washed with brine (15 mL), dried ($MgSO_4$) and concentrated in vacuo. Isolation of boronates **2** was achieved by filtration through a pad of silica gel (hexanes/EtOAc 95:5).
Spectroscopic and analytical data of **2a**: Colourless oil. R_f (hexanes/EtOAc 95:5) = 0.50. $[\alpha]_D$ +45.4 (*c* 1.4, $CHCl_3$). IR (film): 2853 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ 7.30–7.10 (5H, m; ArH), 5.13 (1H, d, J = 2.9 Hz; PhC*H*), 3.86 (1H, dd, J = 8.5 Hz, J = 2.3 Hz; TBSOCHC*H*O), 3.64 (1H, dq, J = 8.5 Hz, J = 6.2 Hz; C*H*OTBS), 2.10–2.00 (1H, m; $CH_3CH(CHOB)_2$), 1.69–1.08 (11H, m; C_6H_{11}), 1.04 (3H, d, J = 6.2 Hz; CH_3CHOTBS), 0.84 (9H, s; $(CH_3)_3CSi$), 0.41 (3H, d, J = 6.8 Hz; $CH_3CH(CHOB)_2$), 0.07 (3H, s; CH_3Si), 0.03 (3H, s; CH_3Si). ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 141.4 (C), 128.1 (CH), 126.9 (CH), 125.3 (CH), 80.7 (CH), 76.6 (CH), 70.3 (CH), 36.2 (CH), 28.4 (CH_2), 28.3 (CH_2), 27.5 (CH_2), 27.4 (CH_2), 27.0 (CH_2), 25.9 (CH_3), 19.5 (CH_3), 18.3 (C), 4.1 (CH_3), −4.4 (CH_3), −5.0 (CH_3). HRMS (+FAB): m/z calcd for $C_{24}H_{42}BO_3Si$ $[M+H]^+$ 417.2996; found 417.2980.

17. (a) Kabalka, G. W.; Shoup, T. M.; Goudgaon, N. M. *J. Org. Chem.* **1989**, *54*, 5930–5933; (b) Molander, G. A.; Bobbitt, K. L. *J. Org. Chem.* **1994**, *59*, 2676–2678; (c) Ramachandran, P. V.; Lu, Z.-H.; Brown, H. C. *Tetrahedron Lett.* **1997**, *38*, 761–764; (d) Martin, H. J.; Drescher, M.; Kählig, H.; Schneider, S.; Mulzer, J. *Angew. Chem., Int. Ed.* **2001**, *40*, 3186–3188.

18. **Method C. General procedure.** To a cooled (0°C) mixture of **2** (0.5 mmol) and NaOAc (82 mg, 1 mmol) in THF/H_2O 3:1 (2.5 mL) was added dropwise H_2O_2 30% (0.65 mL). The reaction mixture was stirred at rt, cooled at 0°C and quenched with sat. Na_2SO_3 (10 mL). The mixture was extracted with CH_2Cl_2 (3×15 mL) and the combined extracts were dried (Na_2SO_4) and concentrated in vacuo. Flash chromatographic purification (hexanes/EtOAc 95:5) afforded the desired diols.
Spectroscopic and analytical data of **3a**: Colourless oil. R_f (hexanes/EtOAc 95:5) = 0.10. $[\alpha]_D$ +17.1 (*c* 2.5, $CHCl_3$). IR (film): 3460 (br), 2923, 1250 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ 7.40–7.20 (5H, m; ArH), 5.01 (1H, d, J = 2.8 Hz; PhC*H*), 3.75 (1H, dq, J = 8.1 Hz, J = 6.2 Hz; C*H*OTBS), 3.60 (1H, dd, J = 8.1 Hz, J = 2.3 Hz; CH(OTBS)C*H*OH), 1.86–1.80 (1H, m; C*H*CH_3), 1.10 (3H, d, J = 6.2 Hz; CH_3CHOTBS), 0.91 (9H, s; $(CH_3)_3CSi$), 0.80 (3H, d, J = 7.0 Hz; CHC*H*$_3$), 0.11 (3H, s; CH_3Si), 0.10 (3H, s; CH_3Si). ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 143.3 (C), 128.0 (CH), 126.8 (CH), 126.0 (CH), 80.6 (CH), 77.9 (CH), 70.4 (CH), 40.8 (CH), 25.8 (CH_3), 19.7 (CH_3), 18.0 (C), 5.0 (CH_3), −4.0 (CH_3), −4.8 (CH_3). HRMS (+FAB): m/z calcd for $C_{18}H_{33}O_3Si$ $[M+H]^+$ 325.2198; found 325.2198.

19. Spectroscopic data of **5a**. ^1H NMR (500 MHz, $CDCl_3$) δ 7.40–7.20 (5H, m; ArH), 5.04 (1H, d, J = 2.1 Hz; PhC*H*), 3.78 (1H, dd, J = 8.1 Hz, J = 2.1 Hz; TBSOCHC*H*O), 3.73 (1H, dq, J = 8.1 Hz, J = 6.0 Hz; C*H*OTBS), 1.75–1.65 (1H, m; C*H*CH_3), 1.52 (3H, s; CH_3CO_2), 1.49 (3H, s; CH_3CO_2), 1.10 (3H, d, J = 6.0 Hz; CH_3CHOTBS), 0.89 (9H, s; $(CH_3)_3CSi$), 0.58 (3H, d, J = 6.8 Hz; CHC*H*$_3$), 0.08 (3H, s; CH_3Si), 0.07 (3H, s; CH_3Si). ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 141.0 (C), 128.0 (CH), 126.8 (CH), 125.6 (CH), 99.2 (C), 78.6 (CH), 74.7 (CH), 69.4 (CH), 35.2 (CH), 29.9 (CH_3), 25.9 (CH_3), 19.5 (CH_3), 18.9 (CH_3), 18.3 (C), 5.2 (CH_3), −4.3 (CH_3), −4.9 (CH_3).