Tetrahedron Letters 50 (2009) 3237–3240

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

Dynamic kinetic asymmetric transformation of 1,4-diols and the preparation of trans-2,5-disubstituted pyrrolidines

Linnéa Borén, Karin Leijondahl, Jan-E. Bäckvall *

Department of Organic Chemistry, Arrhenius Laboratory, Stockholm University, SE-106 91 Stockholm, Sweden

ARTICLE INFO

Article history:
Received 1 December 2008
Revised 16 January 2009
Accepted 3 February 2009
Available online 14 February 2009

ABSTRACT

Dynamic kinetic asymmetric transformation (DYKAT) of a series of 1,4-diols is carried out with Candida antarctica lipase B (CALB), Pseudomonas cepacia lipase II (PS-C II), and a ruthenium catalyst. A β-chloro-substituted 1,4-diol is successfully transformed into an optically pure 1,4-diacetate, which is a highly useful synthetic intermediate. The usefulness of the optically pure 1,4-diacetates is demonstrated by the synthesis of enantiopure 2,5-disubstituted pyrrolidines.

1. Introduction

Enantiopure secondary alcohols can be efficiently synthesized via combined metal- and enzyme-catalyzed dynamic kinetic resolution (DKR).[1–3] We recently demonstrated a laboratory procedure for DKR of 1-phenylethanol on a 150 g to 1 kg scale using low catalytic loading.[4] In a similar manner, enantiopure diols can be synthesized via dynamic kinetic asymmetric transformation (DYKAT).[5–7] Recently, we reported on an efficient procedure for DYKAT of 1,5-diols,[7] using a second generation Ru catalyst system.[2a,8] The enantiopure diacetates obtained were used in the synthesis of enantiopure heterocycles. In this Letter, we report on an efficient DYKAT of both symmetrical and unsymmetrical 1,4-diols and demonstrate their usefulness as synthetic intermediates for the preparation of 2,5-disubstituted pyrrolidines.

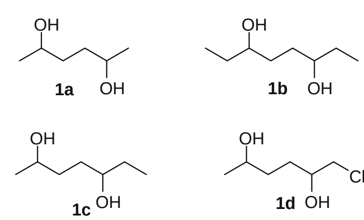
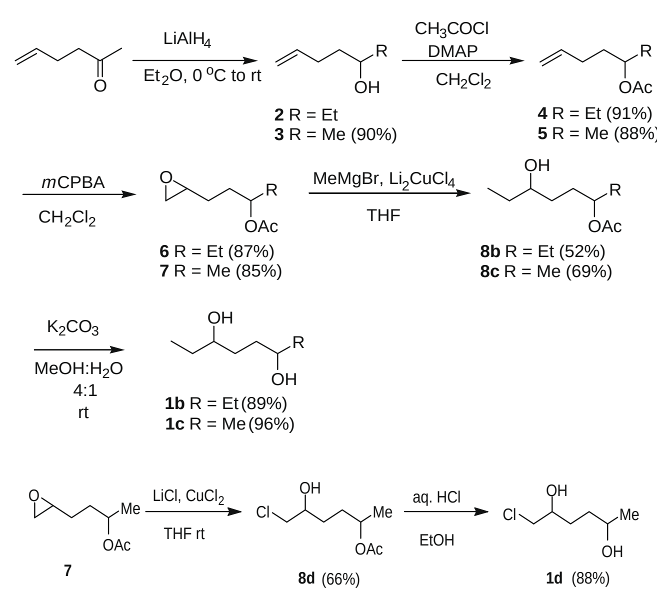


Figure 1. Diols used in the DYKAT.

2. Results and discussion

The diols used in this study for the DYKAT are shown in Figure 1. The symmetrical diols **1a** and **1b** are DL/*meso* mixtures, and the unsymmetrical diols **1c** and **1d** are racemic diastereomeric mixtures. Diol **1a** is commercially available and diols **1b**, **1c,** and **1d** were synthesized from simple starting materials.

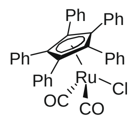
The synthesis of diols **1b**–**d** followed a general pathway (Scheme 1). 6-Hepten-3-ol (**2**) is commercially available and 5-hexen-2-ol (**3**) was readily synthesized via a lithium aluminum hydride reduction of 5-hexen-2-one.[9] The unsaturated alcohols **2** or **3** were acetylated and epoxidized. Acetylation before the epoxidation is crucial to avoid side reactions.[10] The epoxide, **6** or **7**, was then opened with methylmagnesium bromide in a copper-cata-



Scheme 1. Synthesis of starting materials **1b–d**.

* Corresponding author.
E-mail address: jeb@organ.su.se (Jan-E. Bäckvall).

0040-4039/$ - see front matter © 2009 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2009.02.079



9

Figure 2. The epimerization and racemization catalyst.

lyzed reaction, which generated the monoacetate **8b** or **8c**, respectively.

Monoacetate **8d** was obtained by chloride-mediated opening of the epoxide **7**.[11] Monoacetates **8b** and **8c** were hydrolyzed by potassium carbonate in aqueous methanol into the desired diols **1b** and **1c**. However, monoacetate **8d** was hydrolyzed into diol **1d** under acidic conditions to avoid epoxide formation.

Previous studies have shown that *Candida antarctica* lipase B (CALB) is highly enantioselective in catalyzing the acylation of secondary alcohols when a methyl or an ethyl group is present as the medium-sized group according to Kazlauskas' rule.[12] This stereoselectivity has also been extended to diols.[5–7] *Pseudomonas cepacia* lipase, PS-C II, has been used in similar reactions and can also tolerate larger groups as the medium-sized group.[7,13,14] We therefore decided to use these two enzymes in the DYKAT reactions. We recently performed a study on 1,5-diols in which CALB and PS-C II were used together with catalyst **9** (Fig. 2) as an epimerization catalyst.[7] We have now employed the previously optimized DYKAT conditions from that study for the 1,4-diols described here.

The use of CALB and catalyst **9** in the DYKAT of diols **1a**–**c** afforded diacetates **10a**,[15] **10b**, and **10c** in high yields and excellent enantio- and diastereoselectivities (Table 1, entries 1–3). The reason for the formation of some *anti* diacetate is the decrease in selectivity in the second acylation (the acylation of the monoacetate) compared to the first acylation (the acylation of the diol).[16]

Substrate **1d** was diacylated in the DYKAT in high yield and excellent enantioselectivity although the diastereoselectivity was moderate. Previously, we have achieved high selectivity with β-chloroalcohol substrates containing a larger functional group positioned three carbons away from the alcohol moiety.[14] This gave rise to the hypothesis that the stereocenter next to the methyl needs to be acylated first in order to increase the selectivity for the stereocenter next to the chloride.

In order to test this hypothesis, the synthesis of **10d** was modified into stepwise enantioselective acylations of the diol. The first acylation takes place in the synthesis of monoacetate **8d**. Here CALB was employed as the catalyst in the kinetic resolution of 5-hexen-2-ol (**3**).[9] This afforded (2*R*)-acetoxyhexene ((2*R*)-**5**) in 42% yield and 99% ee,[17] which was epoxidized to (2*R*)-**7** and subsequently opened to give monoacetate (2*RS*,5*R*)-**8d** (Scheme 2).[18]

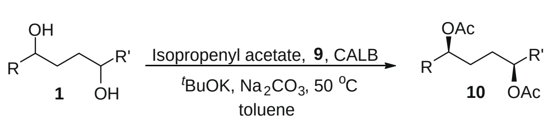
The resulting monoacetate (2*RS*,5*R*)-**8d** was then subjected to a kinetic asymmetric transformation (KAT) using PS-C II as the acylation catalyst. The reaction was fast and highly selective (pseudo $E = 47$), reaching 35% conversion after 4 h reaction time, yielding the enantiopure diacetate (2*S*,5*R*)-**10d** as a 96.6:3.4 *syn*:*anti* mixture (Scheme 3).[19]

When monoacetate (2*RS*,5*R*)-**8d** was subjected to DYKAT conditions, the reaction proceeded with high yield and excellent enantio- and diastereoselectivities (Scheme 4).[20] These results show that the acetate group in monoacetate (2*RS*,5*R*)-**8d** has a positive effect on the stereoselectivity of the acylation of the alcohol moiety next to the chloride.

To demonstrate the utility of the enantiomerically pure diacetates, (*R*,*R*)-**10a** (>99% ee) and (*R*,*R*)-**10b** (>99% ee), they were hydrolyzed to the corresponding diols (*R*,*R*)-**1** and subsequently mesylated. Reaction of the resulting dimesylates (*R*,*R*)-**11a** and (*R*,*R*)-**11b** with sodium tosylamide (NaNHTs) in DMF at 50 °C afforded the corresponding pyrrolidines (*S*,*S*)-**12a** and (*S*,*S*)-**12b** in high yields and without loss of stereochemical information (Scheme 5).

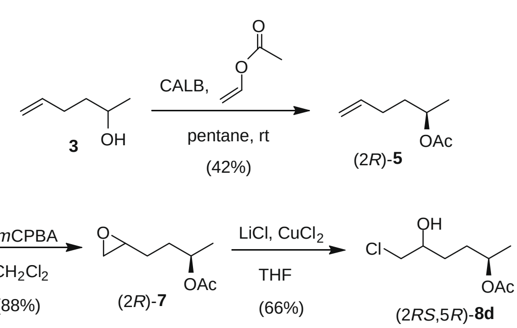
In conclusion, an efficient enantio- and diastereoselective synthesis of 1,4-diol diacetates via DYKAT has been developed. The enantiopure diacetates are useful building blocks for the enantioselective synthesis of important 2,5-disubstituted heterocycles and various ligands.[21] Since a sequential enantioselective acylation can be carried out according to Schemes 2 and 4, diol derivative **10d′** (Fig. 3) with different protecting groups can be obtained. Transformation of the chloroacetate moiety to an epoxide in one step[22] and subsequent ring opening of the epoxide with various nucleophiles[23] would give a 1,4-diol derivative that can be con-

Table 1
DYKAT of 1,4-diols[a]

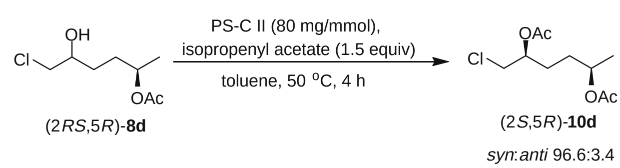


Entry	Diol	Enzyme (mg/mmol **1**)	*t* (h)	ee[b] (%)	*Syn*:*anti*[b]	Yield[b,c] (%)
1	**1a**	CALB (2.5)	24	>99	94:6	98 (82)
2[d]	**1b**	CALB (10)	48	>99	92:8	91 (78)
3	**1c**	CALB (5)	48	>99	95:5	93 (73)
4[e]	**1d**	PS-C II (40)	24	>99	84:16	91 (88)

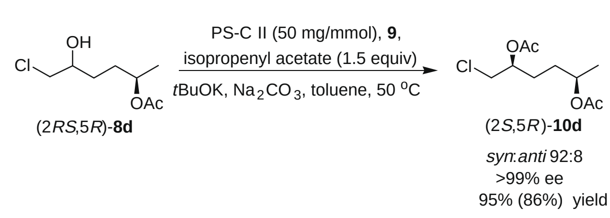
[a] Unless otherwise stated the reactions were performed on a 1 mmol scale in 1 mL of toluene with 3 equiv of isopropenyl acetate, 0.025 equiv of Ru-catalyst **9**, 0.025 equiv of base, and 1 mmol of Na_2CO_3 under argon.
[b] Determined by chiral GC.
[c] Isolated yield in parentheses.
[d] Performed on a 1.7 mmol scale.
[e] The reaction was run on a 1 mmol scale in 2 mL of toluene with 0.05 equiv of Ru-catalyst **9**, 0.05 equiv of base, and 1 mmol of Na_2CO_3 under argon.



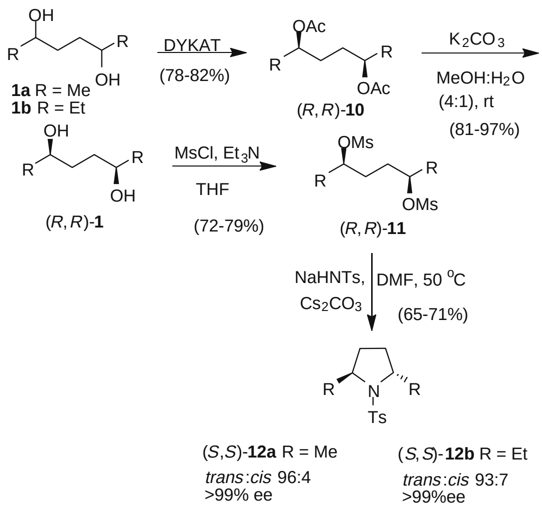
Scheme 2. Synthesis of monoacetate (2*RS*,5*R*)-**8d**.



Scheme 3. KAT of monoacetate (2*RS*,5*R*)-**8d**.



Scheme 4. DYKAT of monoacetate (2*RS*,5*R*)-**8d**.



Scheme 5. Synthesis of pyrrolidines.

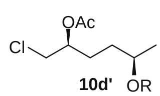


Figure 3. Diol derivative **10d′** with different protecting groups.

verted to enantiomerically pure pyrrolidines. This synthetic approach toward various piperidine derivatives is currently being studied in our laboratory.

3. Procedure for the dynamic kinetic asymmetric transformation (DYKAT) of 1,4-diols

(R,R)-2,5-Diacetoxyhexane **(10a)**. In a general procedure, enzyme (CALB)[24] (2.5 mg), Na_2CO_3 (106 mg, 1.0 mmol), and ruthenium catalyst **9** (16 mg, 0.025 mmol) were added to a flame-dried Schlenk tube under argon. The Schlenk tube was evacuated, filled with argon and toluene (1 mL), placed in a preheated oil bath (50 °C), and a solution of *t*BuOK (0.5 M in THF, 50 µL, 0.025 mmol) was added. The mixture was stirred for 6 min and then diol **1a** (118 mg, 1.0 mmol) was added, and after an additional 4 min, isopropenyl acetate (330 µL, 3 mmol) was added. The mixture was stirred at 50 °C for 24 h then filtered and concentrated. Purification by silica gel column chromatography (pentane:EtOAc 4:1 to EtOAc) afforded **10a** (165 mg, 82%) as an oil. The ee and diastereomeric ratio were determined by chiral GC; >99% ee, *anti:syn* = 94:6. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.21 (6H, d, J = 6.3 Hz, 2 × CH_3), 1.43–1.69 (4H, m, 2 × CH_2), 2.03 (6H, s, 2 × CH_3), 4.90 (2H, m, 2 × CH). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 19.9, 21.3, 31.7, 70.5, 170.7. Spectral data are in accordance with those previously reported.[25]

4. (*S,S*)-2,5-Dimethyl-1-(toluene-4-sulfonyl)-pyrrolidine (12a)

Prepared in three steps: (i) To a stirred solution of diacetate (*R,R*)-**10a** (675 mg, 3.34 mmol) in a 4:1 mixture of MeOH:water (3.6 mL) was added K_2CO_3 (1.38 g, 10 mmol). The mixture was stirred at rt for 3 d, then the MeOH was evaporated and brine was added. The aqueous layer was extracted with EtOAc (10 × 5 mL). The combined organic phases were dried over $MgSO_4$ and concentrated, yielding (*R,R*)-**1a** (384 mg, 97%) which was used without further purification.

(ii) (*R,R*)-**1a** (440 mg, 3.7 mmol) was dissolved in dry THF (40 mL) and cooled to 0 °C. Et_3N (1.8 mL, 12.7 mmol) was added followed by dropwise addition of MsCl (0.98 mL, 12.7 mmol). The resulting mixture was stirred at 0 °C for 1.5 h and then at rt overnight. Water was added and the aqueous phase was extracted with diethyl ether. The combined organic layers were dried over $MgSO_4$ and concentrated. Purification by silica gel column chromatography (pentane/EtOAc 2:1 to EtOAc) afforded the dimesylate (*R,R*)-**11a** (807 mg, 79%) as a white solid.

(iii) The dimesylate (*R,R*)-**11a** (170 mg, 0.62 mmol), NaHNTs (357.5 mg, 1.86 mmol), and Cs_2CO_3 (202 mg, 0.62 mmol) were added to a flame-dried round bottom flask. Dry DMF (4 mL) was added and the resulting mixture was heated at 50 °C for 24 h and was then allowed to cool to rt. Water (10 mL) was added and the mixture was extracted with EtOAc (5 × 20 mL). The combined organic phases were washed with water and brine, dried over $MgSO_4$, and concentrated. Purification by silica gel column chromatography (pentane/EtOAc 4:1 to EtOAc) afforded pyrrolidine (*S,S*)-**12a** (112 mg, 71%) as a white solid. The ee and diastereomeric ratio were determined by chiral GC; >99% ee, trans:cis 96:4. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.19 (6H, d, J = 6.4 Hz, 2 × CH_3), 1.49–1.54 (2H, m, CH_2), 2.04–2.18 (2H, m, CH_2), 2.41 (3H, s, CH_3), 4.02 (2H, m, 2 × CH), 7.24–7.28 (2H, m, Ar–H), 7.69–7.76 (2H, m, Ar–H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 21.3, 21.5, 31.2, 56.2, 127.0, 129.4, 139.9, 142.6.

Spectral data are in accordance with those previously reported.[26]

Acknowledgments

Financial support from the Swedish Foundation for Strategic Research, the Swedish Research Council, and the K & A Wallenberg Foundation is gratefully acknowledged. We thank Amano Europe Ltd for a gift of PS-C 'Amano' II and Johnson Matthey (New Jersey, USA) for a gift of $Ru_3(CO)_{12}$.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2009.02.079.

References and notes

1. (a) Pàmies, O.; Bäckvall, J. E. *Chem. Rev.* **2003**, *103*, 3247–3262; (b) Kim, M. J.; Ahn, Y.; Park, J. *Curr. Opin. Biotechnol.* **2002**, *13*, 578; (c) Pàmies, O.; Bäckvall, J. E. *Trends Biotechnol.* **2004**, *22*, 130–135; (d) Martín-Matute, B.; Bäckvall, J. E. *Curr. Opin. Chem. Biol.* **2007**, *11*, 226–232.
2. (a) Martín-Matute, B.; Edin, M.; Bogár, K.; Kaynak, F. B.; Bäckvall, J.-E. *J. Am. Chem. Soc.* **2005**, *127*, 8817–8825; (b) Martín-Matute, B.; Åberg, J. B.; Edin, M.; Bäckvall, J.-E. *Chem. Eur. J.* **2007**, *13*, 6063–6072.
3. (a) Kim, N.; Ko, S.-B.; Kwon, M. S.; Kim, M.-J.; Park, J. *Org. Lett.* **2005**, *7*, 4523–4526; (b) Norinder, J.; Bogár, K.; Kanupp, L.; Bäckvall, J. E. *Org. Lett.* **2007**, *9*, 5095–5098.
4. Bogár, K.; Martín-Matute, B.; Bäckvall, J. E. *Beilstein J. Org. Chem.* **2007**, *3*, 50.
5. (a) Persson, B. A.; Huerta, F. F.; Bäckvall, J. E. *J. Org. Chem.* **1999**, *64*, 5237–5240; (b) Edin, M.; Martín-Matute, B.; Bäckvall, J. E. *Tetrahedron: Asymmetry* **2006**, *17*, 708–715.
6. Martín-Matute, B.; Edin, M.; Bäckvall, J. E. *Chem. Eur. J.* **2006**, *12*, 6053–6061.
7. Leijondahl, K.; Borén, L.; Braun, R.; Bäckvall, J. E. *Org. Lett.* **2008**, *10*, 2027–2030.
8. For a mechanistic study of the second generation ruthenium catalyst see Ref. 2b.
9. Conti, P.; Dallanoce, C.; De Amici, M.; De Micheli, C.; Carrea, G.; Zambianchi, F. *Tetrahedron: Asymmetry* **1998**, *9*, 657–665.
10. Attempts to epoxidize unsaturated alcohol **3** led to significant amounts of tetrahydrofuran via intramolecular alcohol attack on the epoxide.
11. Hoff, B. H.; Anthonsen, T. *Tetrahedron: Asymmetry* **1999**, *10*, 1401–1412.
12. Kazlauskas, R. J.; Weissfloch, A. N. E.; Rappaport, A. T.; Cuccia, L. A. *J. Org. Chem.* **1991**, *56*, 2656–2665.
13. (a) Rotticci, D.; Haeffner, F.; Orrenius, C.; Norin, T.; Hult, K. *J. Mol. Catal. B: Enzym.* **1998**, *5*, 267–272; (b) Huerta, F. F.; Laxmi, Y. R. S.; Bäckvall, J.-E. *Org. Lett.* **2000**, *2*, 1037–1040.
14. Fransson, A.-B. L.; Borén, L.; Pàmies, O.; Bäckvall, J.-E. *J. Org. Chem.* **2005**, *70*, 2582–2587.
15. Substrate **1a** was previously used in a highly selective DYKAT, see Ref. 6.
16. Nyhlén, J.; Martín-Matute, B.; Sandström, A. G.; Bocola, M.; Bäckvall, J.-E. *ChemBioChem* **2008**, *9*, 1968–1974.
17. This corresponds to an *E*-value of >400.

18. Attempts to replace the KR with a DKR to give (2*R*)-acetoxy-hexene ((2*R*)-**5**) have so far been unsuccessful. Apparently the double bond in hexenol **3** interferes with the racemization catalyst **9**.
19. The reaction was performed on a 0.26 mmol scale, in 1 mL of toluene, at 50 °C under argon. After 4 h, a 35% yield of diacetate (*syn:anti* 96.6:3.4) was obtained, the remainder being monoacetate (*syn:anti* 25.4:74.6).
20. The reaction was performed on a 1 mmol scale in 2 mL of toluene with 1.5 equiv of isopropenyl acetate, 0.05 equiv Ru-catalyst, 0.05 equiv base, and 1 mmol Na_2CO_3, at 50 °C under argon.
21. Burk, M. J. *Acc. Chem. Res.* **2000**, *33*, 363–372.
22. (a) Pàmies, O.; Bäckvall, J.-E. *J. Org. Chem.* **2002**, 9006–9010; (b) Träff, A.; Bogár, K.; Warner, M.; Bäckvall, J.-E. *Org. Lett.* **2008**, *10*, 4807–4810.
23. Archelas, A.; Furstoss, R. *Ann. Rev. Microbiol.* **1997**, *51*, 491–525.
24. Novozyme 435, lipase from (B lipase) *Candida antarctica* produced by submerged fermentation of a genetically modified *Aspergillus oryzae* microorganism and adsorbed on a macroporous resin.
25. Persson, A. B.; Larsson, A. L. E.; Le Ray, M.; Bäckvall, J.-E. *J. Am. Chem. Soc.* **1999**, *121*, 1645–1650.
26. Bäckvall, J.-E.; Schink, H. E.; Renko, Z. D. *J. Org. Chem.* **1990**, *55*, 826–831.