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Synthesis and Enzymatic Kinetic Resolution of α,α-Disubstituted Cyclic Hydroxy Nitriles

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Received December 11, 2003

Abstract: Herein, we describe the diastereoselective synthesis of five- and six-membered α,α-disubstituted cyclic *β*-hydroxy nitriles and their resolution via enzymatic transesterification. By this method, all possible stereoisomers were obtained in enantiopure form and high yield.

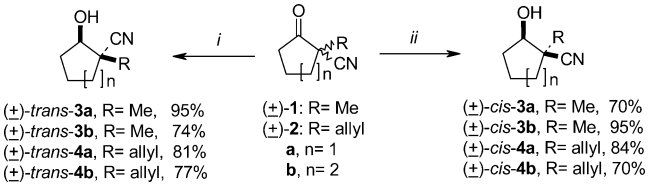
The asymmetric construction of quaternary carbon centers represents a challenging task in organic synthesis.[1] Despite numerous reports on bioreduction of ketones[2] and kinetic resolutions of secondary alcohols, very few strategies utilize these two methods to obtain fully substituted carbon atoms enantiomerically pure, and if so, usually with only moderate success.[3]

On the other hand, the importance of optically active *β*-hydroxy nitriles as suitable synthons for the preparation of *γ*-amino alcohols (like the antidepressant fluoxetine)[4] is steadily growing. Thus, methodologies have been recently developed to prepare these alcohols via classical[5a] or dynamic kinetic resolution,[5b] reduction,[5c] alkylation−reduction,[5d] and addition processes.[5e]

Therefore, we decided to combine both targets and chose racemic *cis*- and *trans*-1-alkyl-2-hydroxycycloalkane nitriles **3** and **4** for the kinetic resolution *via* enzymatic transesterification.

Keto nitriles **1** and **2** were synthesized *via* Thorpe−Ziegler reaction using the corresponding dinitriles followed by alkylation in α-position. After trying different reagents in the subsequent diastereoselective reduction (K-Selectride, $Zn(BH_4)_2$, $CeCl_3/NaBH_4$), Marcantoni's and Bartoli's procedure for the reduction of keto esters[6] gave the best results. $TiCl_4/BH_3$·py was used as the chelating reagent to obtain the trans diastereomers and $CeCl_3$/$LiEt_3BH$ as the nonchelating reagent to obtain the cis diastereomers (Scheme 1).

SCHEME 1[a]



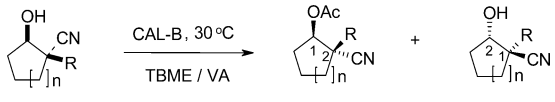
(±)-*trans*-**3a**, R= Me, 95%
(±)-*trans*-**3b**, R= Me, 74%
(±)-*trans*-**4a**, R= allyl, 81%
(±)-*trans*-**4b**, R= allyl, 77%

(±)-**1**: R= Me
(±)-**2**: R= allyl
a, n= 1
b, n= 2

(±)-*cis*-**3a**, R= Me, 70%
(±)-*cis*-**3b**, R= Me, 95%
(±)-*cis*-**4a**, R= allyl, 84%
(±)-*cis*-**4b**, R= allyl, 70%

[a] Reagents and conditions: (i) 1.5 equiv of $TiCl_4$, 1.5 equiv of BH_3·py, DCM, −100 °C, 1 h; (ii) 3.2 equiv of $CeCl_3$, 2 equiv of $LiEt_3BH$, THF, −100 °C, 2 h.

SCHEME 2



(±)-*trans*-**3a**, **b**
(±)-*trans*-**4a**, **b**

(1*R*,2*S*)-**5a**, **b**
(1*R*,2*R*)-**6a**, **b**

(1*R*,2*S*)-**3a**, **b**
(1*S*,2*S*)-**4a**, **b**

Next, we carried out the resolution of racemic *β*-hydroxy nitriles *trans*-**3**, **4** by lipase *Candida antarctica* B (CAL-B)-catalyzed enantioselective acylation using a 3-fold excess of vinyl acetate (VA) as the acyl donor in *tert*-butyl methyl ether (TBME) at 30 °C (Scheme 2). These conditions were chosen since they gave the best results in our previous work on the resolution of cyclic *β*-hydroxy esters.[7]

Under these reaction conditions, *O*-acylation of the trans isomers (±)-**3a**, **3b**, **4a**, and **4b** took place smoothly, and 50% conversion could be reached, yielding both the substrates and the products in excellent enantiomeric excess (ee ≥ 99%), corresponding to excellent enantioselectivities ($E > 200$) in all cases (Table 1). With respect to the ring size and the α-substituent, no difference in the enantioselectivities could be observed. However, CAL-B displayed a lower activity with R = ally than with R = Me (compare entries 1, 2 with 3, 4). Furthermore, CAL-B reacted more sluggishly with the six-membered ring substrates in comparison to their five-membered ring analogues (compare entry 1 with 2, Table 1).

The same methodology was then applied to the cis-configurated *β*-hydroxy nitriles (±)-**3** and (±)-**4** (Scheme 3). In all cases, substrates and products were isolated in very high yield and in excellent enantiomeric excess (ee ≥ 99%, $E > 200$) after 2−13 h (Table 2). Again, no dependence of the enantioselectivity on the ring size was observed. However, a considerably lower activity of CAL-B toward (±)-*trans*-**4a**, **4b** in comparison to substrates (±)-*cis*-**4a**, **4b** was obtained (compare entries 3 and 4 in Tables 1 and 2).

The assignment of the relative configuration of alcohols **4a** and **4b** has been done on the basis of their ^{13}C NMR and ^{1}H-NOESY spectra, as had been previously reported for substrates **3a** and 3**b** (Figure 1).[9] In the case of the

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10.1021/jo035808r CCC: $27.50
Published on Web 02/27/2004

TABLE 1. CAL-B-Catalyzed Enantioselective Acylation of (±)-*trans*-β-Hydroxy Nitriles

					product		substrate			
entry	*n*	R	substrate	*t* (h)	yield[a] (%)	ee[b] (%)	yield[a] (%)	ee[b] (%)	*c*[c] (%)	E[c]
1	1	Me	(±)-*trans*-**3a**	4.0	40.5 (**5a**)	>99	47.0 (**3a**)	>99	50	>200
2	2	Me	(±)-*trans*-**3b**	12.5	40.0 (**5b**)	>99	45.0 (**3b**)	99	50	>200
3	1	allyl	(±)-*trans*-**4a**	34.0	42.5 (**6a**)	>99	48.5 (**4a**)	99	50	>200
4	2	allyl	(±)-*trans*-**4b**	30.0	42 (**6b**)	>99	47.5 (**4b**)	>99	50	>200

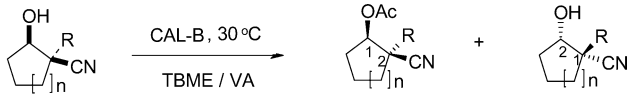
[a] After purification by flash column chromatography on SiO_2. [b] Determined by chiral GC. [c] Calculated from the e.e. of the substrate and the product.[8]

TABLE 2. CAL-B-Catalyzed Enantioselective Acylation of (±)-*cis*-β-Hydroxy Nitriles

					product		substrate			
entry	*n*	R	substrate	*t* (h)	yield[a] (%)	ee (%)[b]	yield[a] (%)	ee[b] (%)	*c*[c] (%)	*E*[c]
1	1	Me	(±)-*cis*-**3a**	4	44.5 (**7a**)	>99	44.0 (**3a**)	>99	50	>200
2	2	Me	(±)-*cis*-**3b**	13	43.0 (**7b**)	>99	44.0 (**3b**)	99	50	>200
3	1	allyl	(±)-*cis*-**4a**	8	35.0[d] (**8a**)	>99	43.5 (**4a**)	>99	50	>200
4	2	allyl	(±)-*cis*-**4b**	8	49.0 (**8b**)	>99	40.5 (**4b**)	>99	50	>200

[a] After purification by flash column chromatography on SiO_2. [b] Determined by chiral GC. [c] Calculated from the ee of the substrate and the product.[8] [d] Some of the product was lost during purification.

SCHEME 3



(±)-*cis*-**3a**, **b** (1*R*,2*R*)-**7a**, **b** (1*S*,2*S*)-**3a**, **b**
(±)-*cis*-**4a**, **b** (1*R*,2*S*)-**8a**, **b** (1*R*,2*S*)-**4a**, **b**

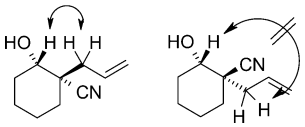


FIGURE 1. Relevant NOESY correlations observed for (±)-*cis*-**4b** and (±)-*trans*-**4b**.

cis isomers (**4a** and **4b**), the CN signal is considerably deshielded in comparison to that of the corresponding *trans* isomer because of the γ steric-compression effect of the vicinal hydroxyl group.[9b] As expected, the opposite effect is observed with the CH_2 group (see the Supporting Information). Also in the NOESY spectrum of compound *cis*-**4b** a correlation between the CH_2 group of the allyl substituent and the CH group of the cycle could be observed confirming the *cis* disposition of these two groups, whereas no correlation was observed between the same protons of the *trans*-**4b** diastereomer.

Regardless of the α-substituent and the ring size, CAL-B only reacted with substrates containing the alcohol with the absolute configuration *R*. In the case of hydroxy nitriles (1*S*,2*S*)-**3a**, **b** and (1*R*,2*S*)-**3a**, **b**, the absolute stereochemistry was assigned by comparison of the sign of their specific rotations with the published data.[9a] The absolute configuration of the enzymatically prepared (1*R*,2*R*)-**6a**,**b** and (1*S*,2*R*)-**8a**,**b** has been tentatively assigned on the basis of two convergent criteria or by a double-confirmation method:[10] (a) the enantiotopic preference displayed by CAL-B in the transesterification of secondary alcohols following in all cases the Kazlauskas's rule;[11] (b) using Mosher's method for secondary alcohols[12] to determine the *S*-configuration of the remaining substrate (1*S*,2*S*)-**4b**. The differential shielding obtained for the α-methylene group of enantiopure Mosher derivative of (1*S*,2*S*)-**4b** and its enantiomer, ($\Delta\delta$ = + 0.05 ppm, signal at 1.98 ppm for the Mosher derivative of (1*S*,2*S*)-**4b** minus the signal at 1.93 ppm for its enantiomer in Mosher derivative of racemic (±)-*trans*-**4b**) obtained from the Mosher derivative of racemic (±)-*trans*-**4b** is in good agreement with previous findings. Where the positive sing of the $\Delta\delta$ values indicates that the product contained the alcohol (*S*)-configurated[10] (see the Supporting Information).

In summary, we have reported a novel resolution of five- and six-membered cyclic β-hydroxy nitriles bearing a quaternary center α to the nitrile utilizing lipase from *Candida antartica* B as the biocatalyst for the enantioselective transesterification of these substrates. This procedure allows, for the first time, a direct access to all 16 stereoisomers of these interesting building blocks in enantiopure form and high yield.

Acknowledgment. We thank Novo Nordisk Co. for the generous gift of Ca lipase. Financial support of this work by the Spanish Ministerio de Ciencia y Tecnología (Project No. PPQ-2001-2683) and by Principado de Asturias (Project No. GE-EXP01-03) is gratefully acknowledged.

Supporting Information Available: ^1H and ^{13}C NMR spectra of new compounds, experimental procedures, and experimental data. This material is available free of charge via the Internet at http://pubs.acs.org.

JO035808R

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