Communications to the Editor

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REDUCTION OF OXIMES OF α-SUBSTITUTED β-KETOESTERS WITH SODIUM CYANOBOROHYDRIDE: STEREOSELECTIVE SYNTHESIS OF 3,4-CIS-SUBSTITUTED AZETIDIN-2-ONES[1)]

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erythro-3-Hydroxyamino-2-alkylbutanoate and its derivatives were prepared stereoselectively by reduction of the oximes of the corresponding β-ketoesters with sodium cyanoborohydride in acidic media. Cyclization of the β-amino acids obtained by reduction and successive hydrolysis gave 3,4-cis-substituted azetidin-2-ones.

KEYWORDS—3,4-cis-substituted azetidin-2-one; erythro-β-amino acid; β-hydroxyiminoester; diastereoselective reduction; sodium cyanoborohydride; diastereofacial selectivity

Though many methods for the introduction of functionalized alkyl groups (e.g. the 1-hydroxyethyl group) into azetidin-2-ones have been described these methods invariably afforded 3,4-trans-azetidin-2-ones. For examples, direct aldol condensation with acetaldehyde[2)] and acetylation followed by reduction[3)] of 4-substituted azetidin-2-ones both proceeded stereoselectively to give thermodynamically more stable trans-3,4-substituted azetidinones, which are used to synthesize thienamycin and related trans-carbapenems. The discovery of carpetimycin A[4)] and its analogues has, however, aroused much interest in the synthesis of 3,4-cis-substituted azetidinones, which can serve as building blocks for these cis-carbapenems. Though several useful methods have been elaborated for construction of cis-azetidinones, they are not so highly stereoselective[5,6)] or have limited utility for introducing a variety of functionalities into the 4-substituent.[7,8)]

In this paper, we report highly stereoselective synthesis of erythro-β-amino acids (D) from α-substituted β-ketoesters (A) which are the important precursors for cis-3,4-azetidin-2-ones. We expected that a six-membered chelate complex (B')

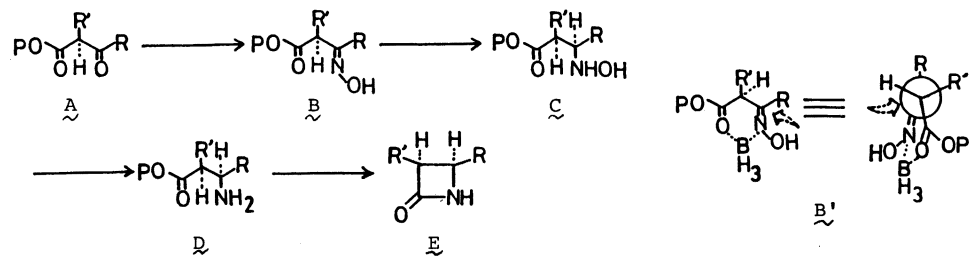

Chart 1 P is a protecting group.

could be formed, when β-hydroxyiminoester (B) is reduced with sodium cyanoborohydride in acidic media, and could control the direction of the attack of the reducing reagent from the less-hindered side giving the desired erythro-β-hydroxyaminoesters (C), whose further hydrogenation over Raney nickel and deblocking of the ester group afford the desired erythro-β-amino acids (D) ready for cyclization to the final azetidinones (E). The advantage of this strategy is obvious, because the desired functionality of R and R' of the starting material (A) can be readily introduced at an early stage.

To verify our strategy, we first examined the synthesis of 3,4-dimethylazetidin-2-one from tert-butyl 2-methylacetoacetate (1). Thus, the oxime (2) was reduced by sodium cyanoborohydride in acidic media at 0°C and the crude product (3) was hydrogenated further over Raney nickel to give a single amino ester (4) as almost the sole product. After acidic hydrolysis of 4, the acid (5) was cyclized by usual method[9] to give azetidinone [6: oil, $\delta(CDCl_3)$: 1.18, d (J=7 Hz, CH_3) and 1.22, d (J=6Hz, CH_3), ν_{CO}=1755 cm^{-1}][10] in 62% yield. A large coupling constant (J=5.0Hz) between protons at the 3- and 4-positions of 6 clearly demonstrates their cis-relationship. A small amount (ca. 1/20 to 6) of another isomer [probably trans-isomer: $\delta(CDCl_3)$: 1.25 (3H, d, J=7Hz), 1.33 (3H, d, J=6Hz), 2.74 (1H, ddq, J=7, 2, 1Hz), 3.36 (1H, dq, J=6, 2Hz)] was detected from the spectrum, whose proportion increased up to ca. 20%, when the reduction step (2→3) was carried out at room temperature.[11] This remarkable stereoselectivity in the reduction step (step b) is due to involvement of the expected cyclic species (B'). Though we tentatively consider borane as the chelating species, proton may also participate in constructing an equally rigid cyclic system.[12]

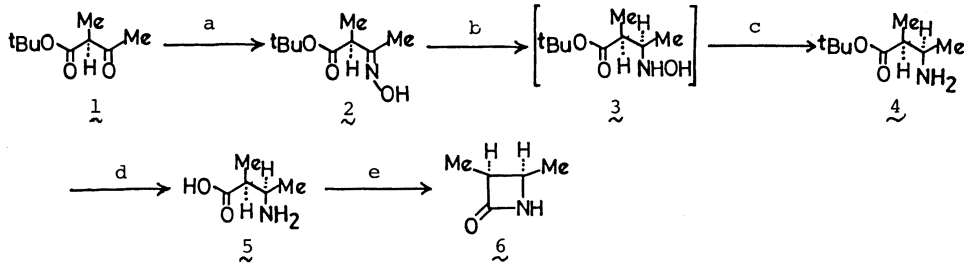

Chart 2 Reagents: a, NH_2OH, MeOH, 0°C; b, $NaBH_3CN$, AcOH-THF(2:1), 0°C; c, H_2, Raney-Ni, MeOH; d, conc. HCl; e, DCC or Ph_3P, $(2\text{-PyS})_2$, CH_3CN

Usual silylation of tert-butyl acetoacetate (7) afforded silyl enol ether (8) as a single isomer[13], which by trimethylsilyl trifluoromethanesulfonate ($TfOSiMe_3$) catalyzed aldol condensation[15] with 2,2-dimethoxypropane led to 2-(1-methoxyisopropyl)acetoacetate [9: oil, $\delta(CDCl_3)$: 1.34 (3H, s, CH_3), 1.37 (3H, s, CH_3), 3.22 (3H, s, OCH_3)]. Conversion of 7 to 10 proceeded in almost quantitative yield.[16] Sequential reactions used to convert 2 to 6 were then applied to 10 to give 3-(1-methoxyisopropyl)-4-methylazetidin-2-one [13: mp 60-61°C, $\delta(CDCl_3)$: 1.49 (3H, d, J=7Hz, CH_3), 3.20 (1H, d, J=5Hz, 3-H), 3.85 (1H, dq, J=5, 7Hz, 4-H)] as the sole product in 32% overall yield from 10. When the reduction step (10 to the hydroxylamine) was carried out at 0°C, no trans-isomer was detected even in the mother liquor fraction of 13. This indicates again that the involvement of cyclic

intermediate (B') is valid and diastereofacial selectivity in the cyclic species is more pronounced when R' becomes more bulky than the methyl group.

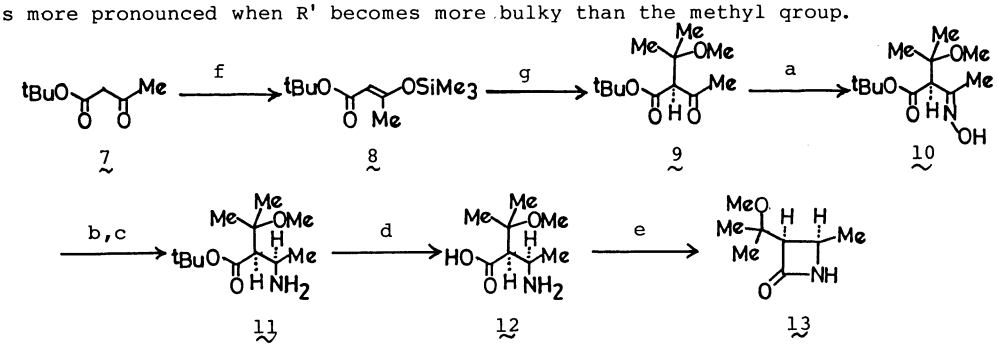

Chart 3 Reagents: a-e are the same in Chart 2; f, Me_3SiCl, Et_3N, THF, reflux; g, $Me_2C(OMe)_2$, $TfOSiMe_3$, CH_2Cl_2, -45°C

The same aldol condensation using acetal (1,1-dimethoxyethane) instead of the ketal also proceeded smoothly. Thus, the two-step procedure using this acetal was applied to 7, the product (14) was obtained in 90% yield as an inseparable mixture of diastereomers in nearly equal amount. The mixture was then transformed to β-lactam (17) in 42% overall yield. Two isomers (both 3,4-cis) were separated by silica gel column chromatography to give a readily crystallizable major one [(S*)-17: mp 62-63°C] and an oily minor one [(R*)-17] in ca. 4:3 ratio.

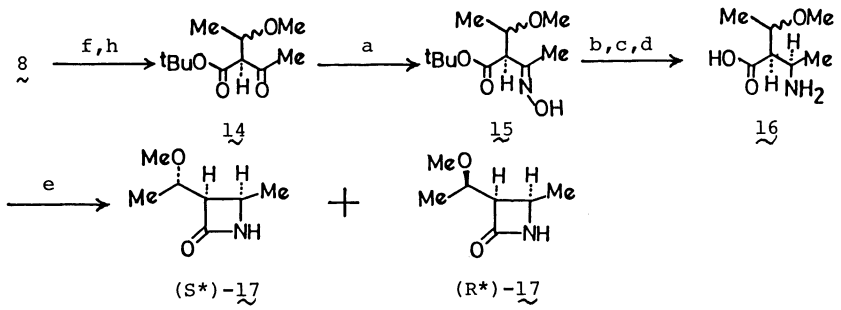

Chart 4 Reagents: a-f are the same in Chart 3; h, $MeCH(OMe)_2$, $TfOSiMe_3$, CH_2Cl_2, -45°C

Inspection of NMR spectra of both isomers ($J_{3,4}$=5.5Hz for both isomers) revealed that the coupling constants C_3 and C_1, are larger (11.0Hz) for the major one than for the minor one (7.0Hz) and these data are in good accordance with those of the related β-lactams reported by McCombie et al.[17] Thus, the relative stereochemistries of both isomers are assigned as (S^*) for the major one and (R^*) for the minor one. It has also been shown that the use of benzyl ester instead of tert-butyl ester likewise proceeds under the same stereocontrol and use of 4-benzyloxyacetoacetates provides 4-benzyloxymethylazetidinones.[18] These facts

suggests that the present methodology can be used for the synthesis of a variety of 3,4-cis-substituted azetidin-2-one derivatives. Further work is now in progress in applying the method to the synthesis of chiral azetidinones.

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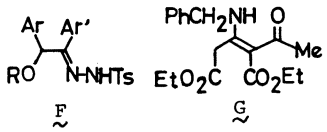
9) Cyclization of these β-amino acids can be effected either by usual DCC method or by Mukaiyama-Ohno's procedure.[a] a: S. Kobayashi, T. Iimori, T. Izawa, and M. Ohno, J. Am. Chem. Soc., 103, 2406 (1981).
10) New compounds were identified by either elemental analysis or by high-resolution mass spectra, and the structures were supported by acceptable spectral data.
11) Actual isolation of the trans-isomer was failed, since it exhibited almost the same property as cis-isomer on chromatography.
12) Almost exclusive formation of the erythro diastereomers has been observed under the same reduction conditions for the systems (F[a] and G[b]). In both cases the unsaturated bond to be reduced has groups capable of complexing with borane (or proton) to form similar cyclic species. a: G. Rosini, A. Medici, and M. Soverini, Synthesis, 1979, 789; b: D. G. Melillo, I. Shinkai, T. Liu, K. Ryan, and M. Sletzinger, Tetrahedron Lett., 21, 2783 (1980).



F G

13) Oil, bp 75-76°C (5mmHg), δ($CDCl_3$): 0.29 (9H, s, $SiMe_3$), 1.49 (9H, s, t-Bu), 2.21 (3H, s, CH_3), 5.04 (1H, s, -CH=). Since tert-butyl formylacetate[14] afforded stereoselectively an [E]-sily enol ether ($J_{2,3}$=12Hz) under the same condition, the stereochemistry of 8 is also assigned as the [E]-isomer.
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16) When 8 reacted with 2,2-dimethoxypropane in the presence of a catalytic amount of $TfOSiMe_3$, a significant amount of the simple hydrolysis product (7) was obtained. Since 7 could be recycled, however, the overall yield of 10 from 7 is almost quantitative based on the consumed 7.
17) S. W. McCombie, A. K. Ganguly, V. M. Girijavallabhan, P. D. Teffrery, S. Lin, and P. Pinto, Tetrahedron Lett., 22, 3489 (1981).
18) Major isomer corresponding to (S*)-cis-form, mp 54.5-56°C, δ($CDCl_3$): 1.31(3H, d, J=6Hz), 3.25 (3H, s), 3.28 (1H, ddd, J=11, 5, 2Hz), 3.59 (1H, t, J=9Hz), 3.64 (1H, dd, J=11, 6Hz), 3.89 (1H, dd, J=9, 3Hz), 3.94 (1H, ddd, J=9, 5, 3Hz), 4.53 (1H, d, J=12Hz), 4.57 (1H, d, J=12Hz), 6.03-6.16 (1H, brs), 7.25-7.30 (5H, m).

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