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REGIO- AND CHEMOSELECTIVE EPIMERIZATION OF *cis*-3-AMINO-β-LACTAMS TO THE *trans*-ISOMERS: A NEW SYNTHESIS OF AZTREONAM

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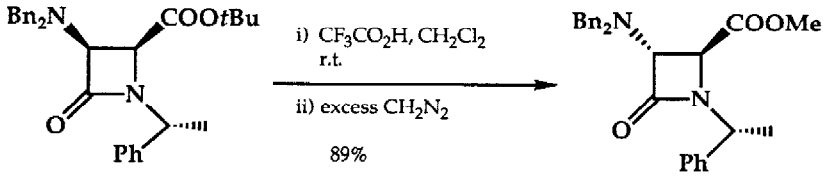
The title isomerization reaction was effected with trifluoroacetic acid and shown to be applicable to the synthesis of an optically active monobactam antibiotic, aztreonam.

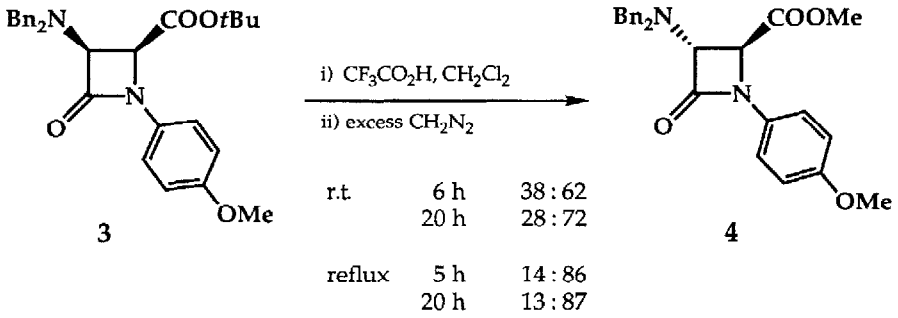
Development of monobactam antibiotics[1,2] has stimulated much interest in the synthesis and the biological estimation of 3,4-disubstituted β-lactams. To evaluate the structure-activity parameter in particular,[1,2] both 3,4-*trans*- and 3,4-*cis*-β-lactams are needed as the biological test samples. Although considerable efforts have been focused on the synthesis of optically active 3,4-*cis*-3-amino-β-lactams,[3] the *trans*-isomers have remained relatively unaccessible.[4] We report herein a method for the synthesis of optically pure 3,4-*trans*-3-amino-β-lactams by regio- and chemoselective epimerization of the corresponding cis-β-lactams. The novel epimerization approach coupled with the *cis*-selective synthesis of monobactams[5] allows us synthesize all stereoisomers of monobactams.

In the course of the synthesis of a monobactam antibiotic carmonam,[5] we studied the hydrolysis of a *t*-butyl ester **1**. After treatment of **1** with trifluoroacetic acid in dichloromethane and then with excess diazomethane, we isolated the methyl ester **2** as the sole product in 89% yield. The relative configuration of **2** was determined to be trans on the basis of $J_{3,4}$ = 2.0 Hz in ^{1}H NMR spectrum.[6] Clearly the epimerization has occurred at C_3 only.[7] Noteworthy is that no epimerization at C_4 was observed even though C_4-*H* is expected to be more acidic than C_3-*H*.[8]

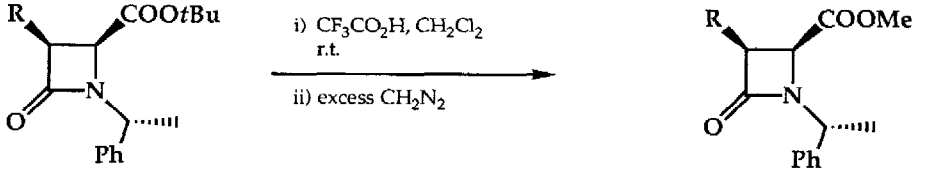


1 **2**

The substituent on the amide nitrogen slightly affected the equilibrium of the isomerization. For example, epimerization of the racemic *N*-*p*-anisidine derivative **3** monitored by ^{1}H NMR was not completed: at room temperature, the ratio of **3** to **4** (and reaction time) was 38 : 62 (6 h) and 28 : 72 (20 h); at the reflux temperature, the equilibration of 14 : 86 was attained in 5 h and did not shift further after 20 h (13 : 87).



To test the functional group compatibility of the epimerization, we treated the *N*-benzyloxycarbonyl derivative 5[9] with trifluoroacetic acid and then with excess diazomethane. Hereby the corresponding methyl ester **6** only was isolated. Thus, an electron-withdrawing Z group on the 3-amino substituent has totally inhibited the epimerization. Retention of the configuration at C_3 was observed again in the reaction of 3-benzyloxyazetidinone 7[10] with trifluoroacetic acid.

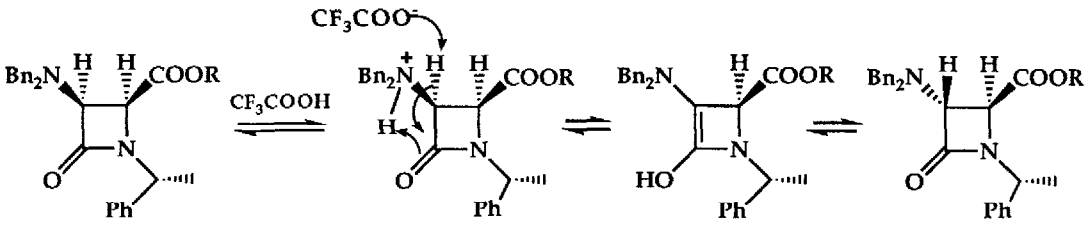


5 R = BnOCONH
7 R = BnO

6 R = BnOCONH 74%
8 R = BnO 78%

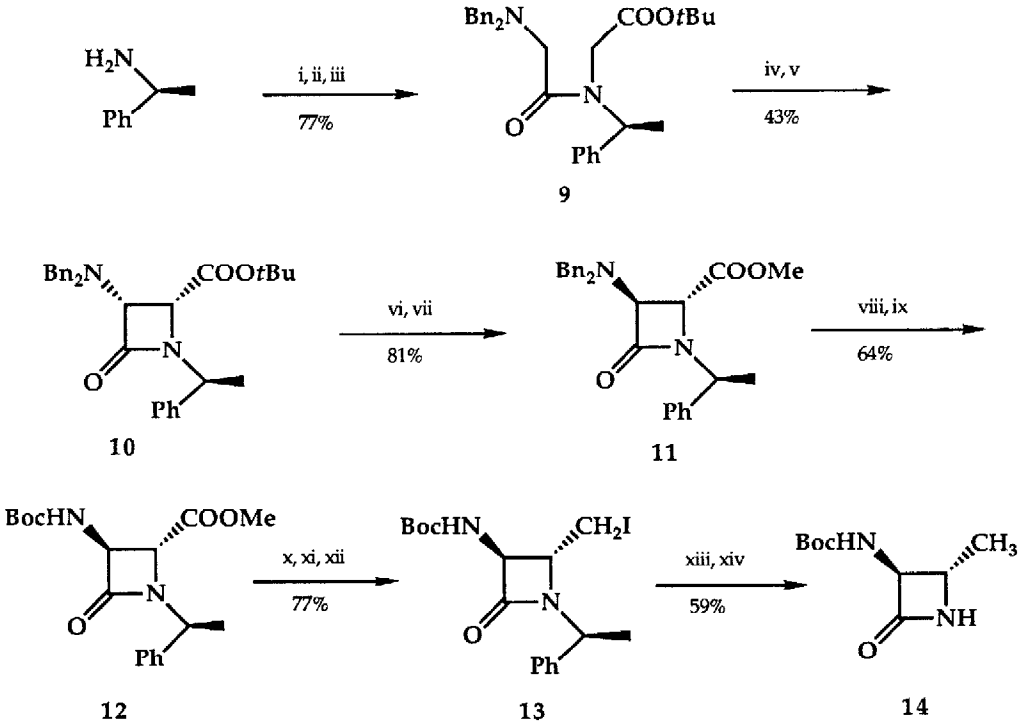
The mechanism of the epimerization is proposed in Scheme I. Protonation at dibenzylamino group readily takes place to increase the acidity of C_3-*H* over C_4-*H*. Subsequent intramolecular prototropy affords an enol form of the azetidinone. Tautomerization of the enol gives thermodynamically favorable *trans*-β-lactam. It is worthy to note that trifluoroacetic acid is a pertinent Brønsted acid which causes enolization only at C_3 with C_4 configuration totally intact. Trimethylsilyl triflate and sodium hydroxide (70 °C) induced random epimerization of both C_3 and C_4 chiral centers.[11,12]

Scheme I



The novel epimerization reaction leading to *trans*-β-lactams was applied to the preparation of a key synthetic intermediate **14** of monobactam antibiotic, aztreonam[13] (Scheme II). Commercially available (*S*)-1-phenylethylamine was transformed to a glycylglycine derivative **9** (77% overall yield). Dianion formation followed by oxidative coupling with *N*-iodosuccinimide (NIS) gave, after chromatographic separation, *cis*-β-lactam **10** (43% yield) in an optically pure form. Treatment of **10** with trifluroacetic acid in dichloromethane at room temperature and then with excess diazomethane gave rise to a *trans*-β-lactam **11** in 81% yield. Removal of the benzyl protecting group by catalytic hydrogenolysis[14] followed by *t*-butoxycarbonylation gave **12** in 64% yield. Reduction of **12** with sodium borohydride in aqueous tetrahydrofuran, tosylation of the resulting alcohol,[15] and subsequent substitution with iodide ion afforded an iodide **13**. The iodomethyl moiety of **13** was converted into methyl with sodium cyanoborohydride. Finally, the chiral auxiliary was removed under the Birch conditions to afford the monobactam intermediate **14** in 59% yield. $[\alpha]_D^{20}$ -67.1° (c 0,14, MeOH) [lit.,[13] $[\alpha]_D^{20}$ -68.4°(c 2.8, MeOH)]. Other spectral data of **14** were fully identical with those reported.[13]

Scheme II



i: $BrCH_2COOtBu$, NEt_3, ii: $BrCH_2COBr$, NEt_3, iii: Bn_2NH, NEt_3, iv: *n*BuLi, TMEDA
v: NIS, vi: CF_3COOH, vii: CH_2N_2, viii: $Pd(OH)_2/C$, H_2, ix: Boc-ON, NEt_3
x: $NaBH_4$, $THF-H_2O$, xi: TsCl, Py, xii: NaI, xiii: $NaBH_3CN$, xiv: Na, NH_3

In summary, 3,4-*trans*-3-amino-β-lactams are readily accessible through epimerization of the corresponding *cis*-β-lactams. Salient features of the present method are high regio- and chemoselectivity. Thus, *trans*-β-lactams were obtained without any loss of optical purity of C_4 chiral center, and the epimerization reaction was successfully applied to the preparation of the key synthetic intermediate **14** of monobactam antibiotic, aztreonam. In addition, the new epimerization methodology presented here coupled with *cis*-selective β-lactam formation allows us to prepare all the stereoisomers of 4-substituted 3-amino-β-lactams (*e.g.* **1, 2, 10,** and **11**).

References and Notes

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7) The absolute configuration of **1** turned out to be (3*S*,4*S*) as disclosed by the transformation to carmonam intermediate.[5] That of **2** was shown to be (3*R*,4*S*), because its enantiomer **11** was successfully converted into **14**.

8) The α-proton of esters is more acidic by 3.0 *pKa* unit than that of *tert.* amides. Cf. F. G. Bordwell and H. E. Fried, *J. Org. Chem.*, **46**, 4327 (1981).

9) Prepared by hydrogenolysis ($HCOONH_4$, 10% Pd/C, EtOH) of **1** followed by benzyloxycarbonylation (BnOCOCl, propylene oxide).

10) Prepared from $BnOCH_2CON(CHMePh)CH_2COOtBu$ by dianion formation, oxidative coupling reaction with NIS followed by separation (cf. Scheme II).

11) A base like DBU, DBN or sodium hydroxide (room temperature) failed to effect noticeable isomerization.

12) Epimerization at C_3 and/or C_4 is effected with a) Me_3SiOTf: T. Chiba and T. Nakai, *Tetrahedron Lett.*, **26**, 4647 (1985), b) NaOH: B. Alcaide, G. Domínguez, G. Escobar, U. Parreño, and J. Plumet, *Heterocycles*, **24**, 1579 (1986), c) DBU: S. Kishimoto, M. Sendai, M. Tomimoto, S. Hashiguchi, T. Matsuo, M. Ochiai, *Chem. Pharm. Bull.*, **32**, 2646 (1984), d) DBN: A. K. Bose, C. S. Narayanan, and M. S. Manhas, *J. Chem. Soc., Chem. Commun.*, 975 (1970).

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