STEREOCHEMISTRY IN BOROHYDRIDE REDUCTION OF 7-IMINO-CEPHEMS: AN IMPROVED METHOD FOR CONVERSION OF THE 7α-AMINO- 1-OXA(THIA)CEPHEMS INTO THE 7β-AMINO ISOMERS

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Abstract — Sodium cyanoborohydride in methanol containing hydrogen chloride (pH ~3) proved to be an excellent reagent system for smooth and highly stereoselective reduction of the 7-imino-1-oxa(thia)cephems **6** or their equivalent 7-methoxy amines **8** to the corresponding 7β-amines **2**. Borane-pyridine ($H_5C_5N{\cdot}BH_3$) or borane-trimethylamine complex [$(CH_3)_3N{\cdot}BH_3$] is also useful, although less efficient. The imines **6** or the methoxy amines **8** were formed simply by hydrogen chloride catalyzed methanolysis of the methylsulfenylimino derivatives **9**. The experimental conditions were common to the above reduction process and, thus, both the methanolysis and the reduction could be performed in one pot. Combination of this one-pot procedure for the conversion of the sulfenylimines **9** into the 7β-amines **2** with the procedure for the preparation of **9** from the 7α-amines **1** provided an improved general method for the preparation of biologically important 7β-amino-1-oxa(thia)cephems from the corresponding 7α-amines **1**.

Highly stereoselective conversion of 7α-aminocephems **1** into their 7β-amino isomers **2** has been of continuous importance in syntheses, particularly in total syntheses of various natural and unnatural cephem nuclei.[1] We have been concerned with this problem and published a practical procedure for the conversion of 7α-amino-1-oxa(thia)cephems into the 7β-amino isomers, which involved a four-step reaction sequence, *i.e.* formation of a 7α Schiff base **3** with chloral, 1,4-dehydrochlorination, borohydride reduction and subsequent acid hydrolysis, as shown in Chart 1.[2] We also reported that sodium or potassium borohydride reduction of **4** proceeded in a highly stereoselective manner, as evidenced from the fact that the reduction product **2** formed in a very high yield contained no 7α-amino isomer. We suggested that this high

This paper is dedicated to Professor Sir Derek Barton on the occasion of his 70th Birthday.

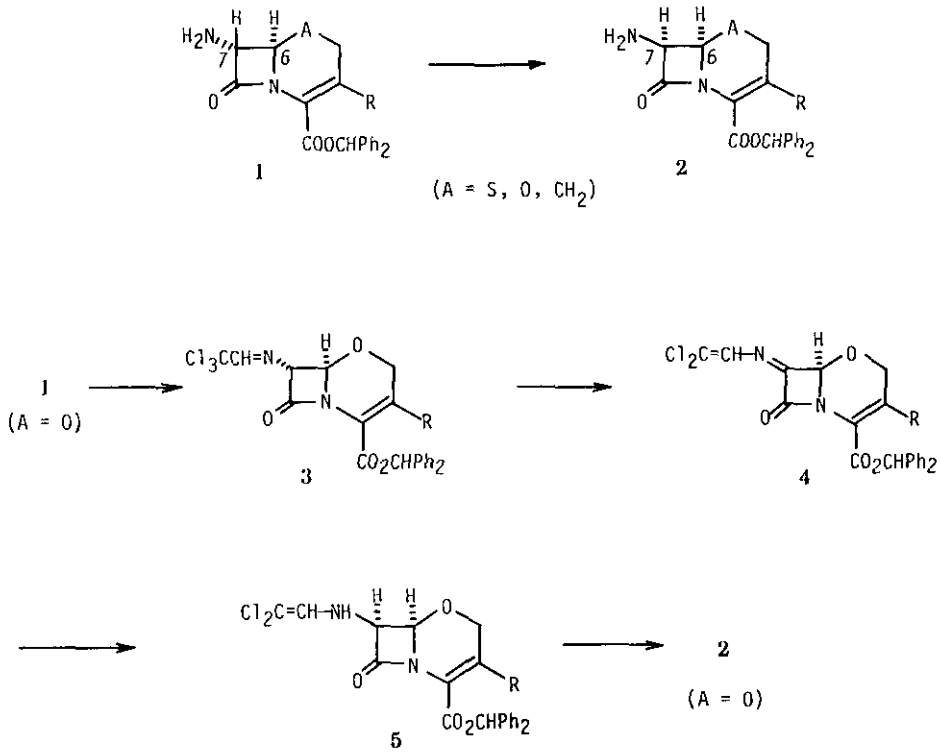


Chart 1

stereoselectivity was due to the steric control by the bulky dichlorovinyl group attached to the imino nitrogen in 4, thus effectively causing the borohydride reagent to approach from the less hindered α-side.[2] This rationalization was based upon the observation that, in contrast with 4 (R = 1-methyl-5-tetrazolylthiomethyl), the unsubstituted imino analog **6a**, prepared *in situ* by N-chlorination of **1a** with *tert*-butyl hypochlorite followed by dehydrochlorination with lithium methoxide in methylene chloride and methanol, gave a 1:1 mixture of 7α- and 7β-amines, **1a** and **2a**, by potassium borohydride reduction.[3] We have now found that the stereochemical course of the reduction is dramatically influenced by the reagent system varying from potassium borohydride in methylene chloride-methanol to sodium cyanoborohydride in methanol-hydrogen chloride (pH ~3) which gave the 7β-amine **2a** (isolated as phenylacetamide **7a**) as a sole reduction product in high yield. This finding led us to establish an efficient and convenient procedure for the conversion of the 7α-amino-1-oxa(thia)cephems into the 7β-amino isomers. In this communication we wish to describe this procedure in some details.

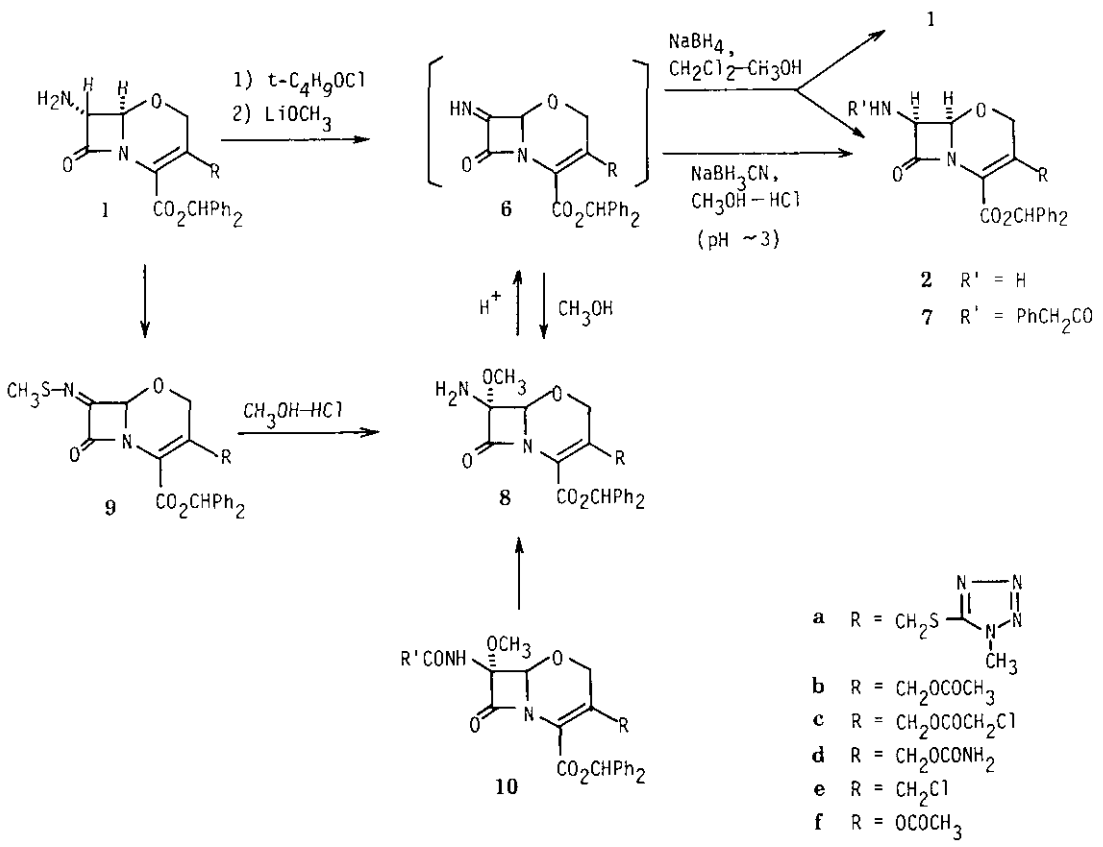
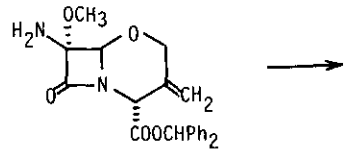


Chart 2

We anticipated that 7-imino-1-oxacephem **6a** could be reduced more smoothly with sodium cyanoborohydride *in an acid medium than with sodium or potassium* borohydride, as was the case in borohydride reduction of alkyl or aryl imino derivatives, RN=CR'R". In carrying out the experiment we used 7β-amino-7α-methoxy-1-oxacepehms **8** as the substrates in place of the labile and hardly isolable 7-imino-1-oxacephems **6** which were conveniently formed as an equilibrium component[4] when a methanol solution of the former was treated with an acid, *e.g.*, hydrogen chloride, as illustrated in Chart 2. The 7β-amino-7α-methoxy-1-oxacephems **8** were available from the corresponding 7β-acylamino-1-oxacephamycin derivatives **10** by the conventional deacylation method using phosphorus pentachloride or, more conveniently, from the sulfenyl imino compounds **9** by treating with methanolic hydrogen chloride as discussed in detail later. Sodium cyanoborohydride reduction of 7-methoxy amine **8a**,[5] readily available from the corresponding 7β-benzoylamino derivative **10a** (R' = C_6H_5), was investigated first. Thus, to the methoxy amine **8a** dissolved in methanolic hydrogen chloride (1.5 mol. equiv.) were added under ice-cooling

and stirring sodium cyanoborohydride (2.0 mol. equiv.) and a trace amount of methyl orange as a pH indicator and the reaction mixture was stirred at 0°C for 3.5 h. Throughout the reaction 2 N methanolic hydrogen chloride (1.8 mol. equiv. in total) was added occasionally to keep the red color of the solution persisting. Neutralization with sodium bicarbonate, extraction with ethyl acetate and the subsequent work-up gave the crude amine **2a** which was purified as its crystalline phenylacetamide derivative **7a**. The yield was 90% from **8a**. Similar results were also obtained with other methoxy amines of different structures, **8d**, **11** and **14** (a 2.5:1 mixture of 7α-methoxy-7β-amine and its epimer), giving, the 7β-amines



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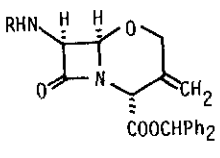
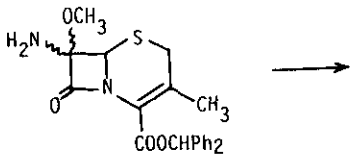


12 R = H
13 R = $PhCH_2CO$



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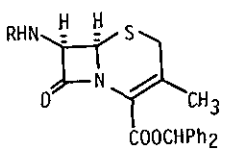


15 R = H
16 R = $PhCH_2CO$

2d, **12** and **15**, respectively, in good or high yields, which were characterized as their phenylacetamide derivatives **7d**, **13** and **16**. It should be emphasized that in all cases, exclusive formation of the 7β-amines was observed and, thus, the procedure proved valuable for stereoselective preparation of the biologically important 7β-amines from the corresponding methoxy amines. Moreover, the results demonstrate that the present procedure can be applied broadly for reduction of the methoxy amines of various cephem nuclei.

In order to gain some insight into the stereochemical mode of the reaction as well as for large scale preparation we further investigated usefulness of other borohydride reagents. We found that borane-pyridine ($H_5C_5N{\cdot}BH_3$) and borane-trimethylamine complex [$(CH_3)_3N{\cdot}BH_3$] were found to be useful, although the reductions with these reagents, particularly with $(CH_3)_3N{\cdot}BH_3$, were somewhat sluggish and needed higher temperature and prolonged reaction time. These results were summarized in Table 1.

As mentioned above, the unique stereochemical outcome is characteristic of this reduction procedure and following arguments (Chart 3) may serve, at least in part, for understanding these unique results. It is reasonably assumed[6] that in an acid medium at pH 3 sodium cyanoborohydride produces some kind of molecular species, most probably a molecular complex of hydrogen cyanide and borane as expressed by the

Table 1. Reduction of cephem 7-methoxy amines with sodium cyanoborohydride and related reagents to 7β-amines (or their phenylacetamido derivatives)

7-Methoxy-amine	Reagent	Conditions Time (h)	Conditions Temp. (°C)	Product[7] 7β-Amine (yield, %)	Product[7] Phenylacetamide (yield, %)
8a	$NaBH_3CN$	3.5	0	--	**7a** (90)
8a	$H_5C_5N{\cdot}BH_3$	5.0	0-25	**2a** (94)	--
8a	$(CH_3)_3N{\cdot}BH_3$	3.0	25	--	**7a** (60)
8d	$NaBH_3CN$	3.0	0	--	**7d** (58)
11	$NaBH_3CN$	3.0	0	--	**13** (96)
14	$NaBH_3CN$	2.0	0	--	**16** (94)

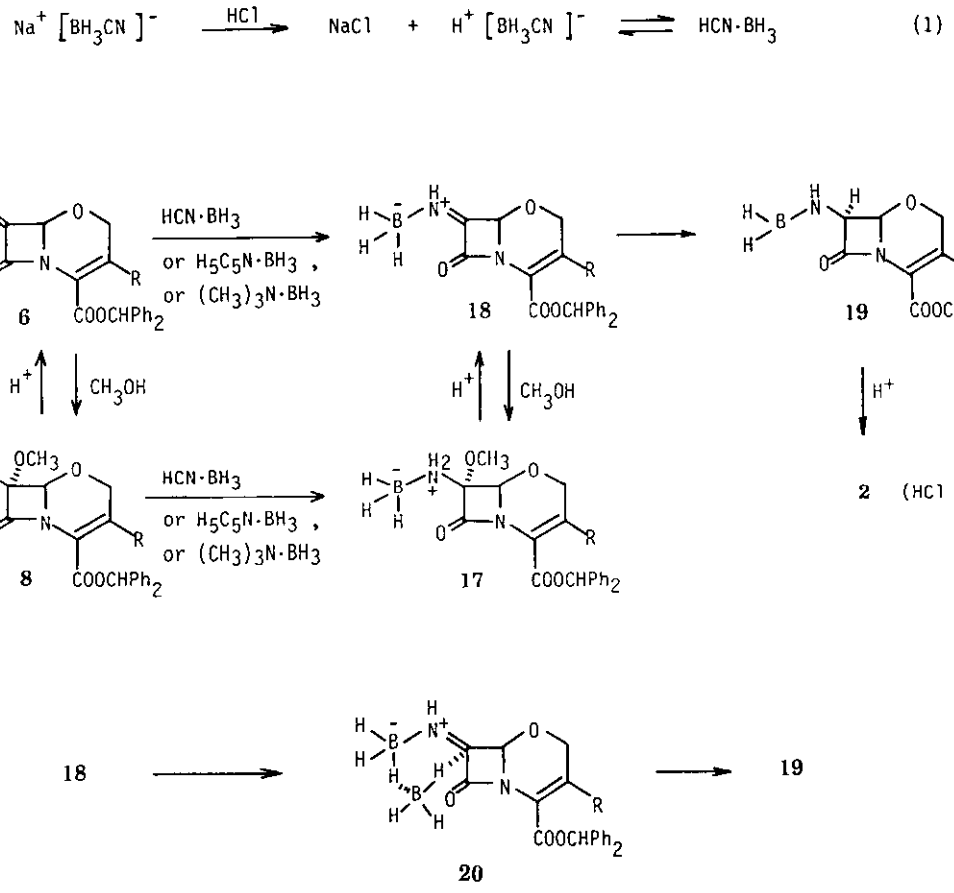


Chart 3

formula, $HCN{\cdot}BH_3$, via the initially formed conjugate acid, $H^+[BH_3CN]^-$ [equation (1)]. The formulation of $HCN{\cdot}BH_3$ is based upon an analogy to the borane-*tert*-amine complexes, such as $C_5H_5N{\cdot}BH_3$ and $(CH_3)_3N{\cdot}BH_3$, and may not be so arbitrary if we consider that hydrogen cyanide will react with borane as a Lewis base. This molecular complex may undergo displacement reaction[6] with either 7-methoxy amine **8** or 7-imine **6** to form an exchanged complex, **17** or **18**, respectively (Chart 3). These products can be formed also by displacement reaction of **8** or **6** with $C_5H_5N{\cdot}BH_3$ or $(CH_3)_3N{\cdot}BH_3$ as shown in Chart 3. The complex **17** can be converted into the imine-borane complex **18** and this intermediate complex undergoes reduction with intramolecular hydride migration either directly or more probably via a six-membered transition state **20**. The hydride migration should occur from the less hindered α-side.[8] This postulation can also rationalize why the reduction with $H_5C_5N{\cdot}BH_3$ or $(CH_3)_3N{\cdot}BH_3$ proceeded slowly. With these relatively stable complexes, exchange reactions to form **17** and **18** are slower than with borane-hydrogen cyanide complex.

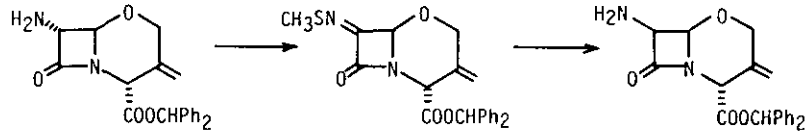
Our next subject was to develop an efficient dehydrogenation process for converting 7α-aminocephems **1** to 7-imines **6** or 7-methoxy amines **8**. The process, when coupled with the newly developed reduction procedure discussed above, should complete a new and efficient route to 7β-aminocephems **2** from their 7α-epimers **1**. We found that dehydrogenation of **1** was most conveniently achieved via the methylsulfenylimines **9**, which, on treatment with methanolic hydrogen chloride, were smoothly converted into the methoxy amines **8**. The solvent system containing hydrogen chloride was the same as that used for the sodium cyanoborohydride reduction, and, therefore, the two reactions were carried out continuously in one pot, that is, there was no need to isolate the intermediately formed methoxy amines **8**. Thus, a number of methylsulfenylimino-1-oxacephems **9** and 3-exomethylenecepham **22** were smoothly converted into the corresponding 7β-amines **2** (characterized as their phenylacetamido derivatives **7**) and **12**, respectively. The methylsulfenylimines **9** and **22** were conveniently prepared from the corresponding 7α-amines **1** and **21** by applying the Squibb procedure[9] involving treating the amines with methylsulfenyl chloride (3 mol. equiv.) in the presence of propylene oxide and molecular sieve. These results listed in Table 2 clearly demonstrate that the present two-step conversion provides a new and generally applicable method for the preparation of the biologically important 7β-amino-1-oxa- or 1-thiacephems from the corresponding 7α-isomers. We believe that this method is superior to the previously reported method[2] in view of the number of steps and yield in the conversion. In the following is given a representative example for the present procedure.

21 → **22**: To a mixture of 3-exomethylene-7α-amino-1-oxacephem **21** hydrochloride (2 g, 5 mmol), propylene oxide (20 ml), molecular sieve (Linde, Type 4A, 15 g) and methylene chloride (80 ml) was added 1 M solution of methylsulfenyl chloride in carbon tetrachloride (25 ml, 5 mol. equiv.). The resulting mixture was stirred under ice-cooling for 2 h. The molecular sieve was filtered off, the filtrate was distilled under

Table 2. Conversion of 7α-amino-1-oxacephems 1 and 1-oxacepham 21 into the corresponding 7β-amino derivatives 7 and 12 via the methylsulfenylimino derivatives 9 and 22

7α-Amines	Sulfenylimine[10] (yield, %)	7β-Amino deriv.[a)11] (yield, %)
1b *1	**9b** (75)	**7b** (73)
1c *2	**9c** (65)	**7c** (90)
1e *1	**9e** (—)[b)]	**7e** (57)[c)]
1f *1	**9f** (70)	**7f** (83)
21 *1	**22** (91)	**12** (82)[d)]

a) Sodium cyanoborohydride was used as reducing agent except for the conversion of **22** to **12**.
b) Crude **9e** was used for the reduction step.
c) The yield was based upon the 7α-amine **1e**.
d) Borane-pyridine complex ($BH_3 \cdot NC_5H_5$) was used for reduction.
*1 Prepared from the corresponding benzoylamide, respectively, of **1b** (T. Aoki et al., Heterocycles, 1981, 15, 409), **1e** and **21** (Reference 5) and **1f** (T. Aoki et al., Heterocycles, 1982, 18, 201).
*2 Prepared in a similar way to the preparation of **1b**.



21 **22** **12**

reduced pressure and the residue was chromatographed (silica gel, benzene-ethyl acetate 9 : 1) to give 7-methylsulfenylimino-1-oxacepehm **22** (1.86 g, 91%).

22 → **12**: 7-Methylsulfenylimino-1-oxacephem **22** (1 g, 2.45 mmol) was dissolved in anhydrous methanol (8 ml) and 2 N methanolic hydrochloric acid (2 ml, 1.63 mol. equiv.), and the resulting solution was stirred under ice-cooling for 40 min. To this solution were added borane-pyridine complex (227 mg, 2.45 mmol) and a trace of methyl orange and the resulting red-colored solution was stirred at 15-18°C for 2 h. During the reaction 2 N methanolic hydrochloric acid (1.4 ml in total) was added in four portions to maintain the red color. The solution was condensed under reduced pressure, poured into ice-water containing sodium bicarbonate and extracted with methylene chloride. The usual work-up gave pure 7β-amino-1-oxacephem **12** (732 mg, 82%) after silica gel chromatography.

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6. See the discussions in the following literatures: a) R. C. Wade, E. A. Sullivan, J. R. Bershied, Jr., and K. F. Purcell, Inorganic Chemistry, 1970, 9, 2146. b) J. R. Berschied, Jr. and K. F. Purcell, ibid., 1970, 9, 624.
7. Physical data of 7β-amino derivatives are listed below. **2a**: mp 165°C; ir (Nujol) 1775, 1715 cm^{-1}; nmr ($CDCl_3$-CD_3OD) δ 3.83 (3H, s, NCH_3), 4.25 (2H, s, H-3'), 4.48 (1H, d, J = 4 Hz, H-7), 4.59, 4.69 (2H, ABq, J = 12 Hz, H-2), 5.01 (1H, d, J = 4 Hz, H-6), 6.90 (1H, s, Ar_2CH), 7.2-7.6 (10H, m, C_6H_5). **7a**: mp 197°C; ir (Nujol) 3320, 1785, 1705, 1653 cm^{-1}; nmr ($CDCl_3$) δ 3.60 (2H, s, $ArCH_2$), 3.76 (3H, s, NCH_3), 4.21 (2H, s, H-3'), 4.60, 4.48 (2H, ABq, J = 19 Hz, H-2), 4.96 (1H, d, J = 4 Hz, H-6), 5.70 (1H, dd, J = 10, 4 Hz, H-7), 6.38 (1H, d, J = 10 Hz, CONH), 6.88 (1H, s, Ar_2CH), 7.15-7.65 (15H, m, C_6H_5). **7d**: Ir ($CHCl_3$) 3500, 3420, 1785, 1720, 1675 cm^{-1}; nmr ($CDCl_3$) δ 3.58 (2H, s, $ArCH_2$), 4.29 (2H, s, H-2), 4.75-5.18 (5H, m, H-3', H-6, $CONH_2$), 5.65 (1H, dd, J = 10, 4 Hz, H-7), 6.54 (1H, d, J = 10 Hz, CONH), 6.85 (1H, s, Ar_2CH), 7.15-7.60 (15H, m, C_6H_5). **13**: Ir ($CHCl_3$) 3400, 1770, 1733, 1673 cm^{-1}; nmr ($CDCl_3$) δ 3.55 (2H, s, $ArCH_2$), 4.21 (2H, s, H-2), 5.06 (1H, s, H-4), 5.21 (1H, d, J = 4 Hz, H-6), 5.27 (2H, s, $C=CH_2$), 5.52 (1H, dd, J = 10, 4 Hz, H-7), 6.22 (1H, d, J = 10 Hz, CONH), 6.85 (1H, s, Ar_2CH), 7.20-7.40 (15H, m, C_6H_5). **16**: Ir (Nujol) 3250, 1760, 1710, 1650 cm^{-1}; nmr (CD_3SOCD_3-CD_3OD) δ 2.03 (3H, s, CH_3), 3.40, 3.57 (2H, ABq, J = 22.5 Hz, H-2), 3.57 (2H, s, $ArCH_2$), 5.06 (1H, d, J = 4 Hz, H-6), 5.68 (1H, dd, J = 10, 4 Hz, H-7), 6.90 (1H, s, Ar_2CH), 7.2-7.6 (15H, m, C_6H_5), 9.05 (1H, d, J = 10 Hz, CONH).
8. The generally accepted mechanism of sodium cyanoborohydride reduction provides another possible reaction pathway. Thus, proton activates the imino group to give the imminium ion (H instead of H_3B^- in **18** in Chart 3) which is then attacked by BH_3CN^- to form **19**. However, this mechanism hardly explains the observed high stereoselectivity in the reduction.
9. E. M. Gordon, H. W. Chang, C. M. Cimarusti, B. Toeplitz, and J. Z. Gougoutas, J. Am. Chem. Soc., 1980, 102, 1690.
10. Physical data of methylsulfenylimino derivatives are listed below. **9b**: Ir ($CHCl_3$) 1780, 1730 cm^{-1}; nmr ($CDCl_3$) δ 1.99 (3H, s, $COCH_3$), 2.86 (3H, s, SCH_3), 4.48 (2H, s, H-2), 4.95, 5.16 (2H, ABq, J = 14

Hz, H-3'), 5.32 (1H, brs, H-6), 6.93 (1H, s, $Ar_2C\underline{H}$), 7.20-7.80 (10 H, m, $C_6\underline{H}_5$). **9c**: Ir ($CHCl_3$) 1780, 1720 cm^{-1}; nmr ($CDCl_3$) δ 2.86 (3H, s, $SC\underline{H}_3$), 3.96 (2H, s, $C\underline{H}_2Cl$), 4.50 (2H, s, H-2), 5.07, 5.27 (2H, ABq, J = 14.4 Hz, H-3'), 5.34 (1H, brs, H-6), 6.92 (1H, s, $Ar_2C\underline{H}$), 7.30-7.70 (10H, m, $C_6\underline{H}_5$). **9f**: mp 142°C; ir ($CHCl_3$) 1775, 1725, 1635 cm^{-1}; nmr ($CDCl_3$) δ 2.03 (3H, s, $COCH_3$), 2.85 (3H, s, SCH_3), 4.37 (2H, s, H-2), 5.42 (1H, brs, H-6), 6.92 (1H, s, $Ar_2C\underline{H}$), 7.20-7.60 (10H, m, $C_6\underline{H}_5$). **22**: Ir ($CHCl_3$) 1775, 1740 cm^{-1}; nmr ($CDCl_3$) δ 2.76 (3H, s, SCH_3), 4.24 (2H, s, H-2), 5.72, 5.79, 5.82 (3H, each s, H-3, H-4, -$C=C\underline{H}_2$), 5.67 (1H, brs, H-6), 6.88 (1H, s, $Ar_2C\underline{H}$), 7.20-7.40 (10H, m, $C_6\underline{H}_5$).

11. Physical data of 7β-amino derivatives are listed below. **7b**: Ir ($CHCl_3$) 3410, 1790, 1730, 1680 cm^{-1}; nmr ($CDCl_3$) δ 1.96 (3H, s, $COC\underline{H}_3$), 3.60 (2H, s, H-2), 4.29 (2H, s, H-2), 4.91, 5.13 (2H, ABq, J = 14 Hz, H-3'), 4.92 (1H, d, J = 4 Hz, H-6), 5.68 (1H, dd, J = 10, 4 Hz, H-7), 6.48 (1H, d, J = 10 Hz, $CON\underline{H}$), 7.20-7.60 (15 H, m, $C_6\underline{H}_5$). **7c**: Ir ($CHCl_3$) 1785, 1715, 1670 cm^{-1}; nmr ($CDCl_3$) δ 3.62 (2H, s, $ArC\underline{H}_2$), 3.93 (2H, s, $COC\underline{H}_2Cl$), 4.29 (2H, s, H-2), 4.92 (1H, d, J = 4 Hz, H-6), 5.00, 5.23 (2H, ABq, J = 13.5 Hz, H-3'), 5.67 (1H, dd, J = 10, 4 Hz, H-7), 6.45 (1H, d, J = 10 Hz, $CON\underline{H}$), 6.88 (1H, s, $Ar_2C\underline{H}$), 7.20-7.60 (15H, m, $C_6\underline{H}_5$). **7e**: Ir ($CHCl_3$) 3400, 1790, 1720, 1670 cm^{-1}; nmr ($CDCl_3$) δ 3.60 (2H, s, $ArC\underline{H}_2$), 4.35 (2H, s, H-2), 4.37, 4.51 (2H, ABq, J = 12.5 Hz, H-3'), 4.95 (1H, d, J = 4 Hz, H-6), 5.66 (1H, dd, J = 10, 4 Hz, H-7), 6.30 (1H, d, J = 10 Hz, $CON\underline{H}$), 6.88 (1H, s, $Ar_2C\underline{H}$), 7.20-7.50 (15 H, m, C_6H_5). **7f**: Ir ($CHCl_3$) 3420, 1800, 1726, 1685 cm^{-1}; nmr ($CDCl_3$) δ 1.99 (3H, s, $COC\underline{H}_3$), 3.57 (2H, s, $ArC\underline{H}_2$), 4.21 (2H, s, H-2), 5.00 (1H, d, J = 4 Hz, H-6), 5.63 (1H, dd, J = 10, 4 Hz, H-7), 6.36 (1H, d, J = 10 Hz, $CON\underline{H}$), 6.88 (1H, s, $Ar_2C\underline{H}$), 7.20-7.50 (15 H, m, $C_6\underline{H}_5$). **12**: Ir ($CHCl_3$) 3380, 1760,1732 cm^{-1}; nmr ($CDCl_3$) δ 1.66 (2H, brs, $N\underline{H}_2$), 4.30 (2H, s, H-2), 4.30 (1H, d, J = 4 Hz, H-7), 5.12-5.30 (4H, m, H-4, H-6, $C=C\underline{H}_2$), 6.86 (1H, s, $Ar_2C\underline{H}$), 7.20-7.40 (10 H, m, $C_6\underline{H}_5$).

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