

STEREOCHEMISTRY IN BOROHYDRIDE REDUCTION OF 7-IMINO-
CEPHEMS: AN IMPROVED METHOD FOR CONVERSION OF THE
7 α -AMINO- 1-OXA(THIA)CEPHEMS INTO THE 7 β -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 7 β -amines **2**. Borane-pyridine ($\text{H}_5\text{C}_5\text{N}\cdot\text{BH}_3$) or borane-trimethylamine complex $[(\text{CH}_3)_3\text{N}\cdot\text{BH}_3]$ is also useful, although less efficient. The imines **6** or the methoxy amines **8** were formed simply by hydrogen chloride catalyzed methanolysis of the methylsulfonylimino 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 sulfonylimines **9** into the 7 β -amines **2** with the procedure for the preparation of **9** from the 7 α -amines **1** provided an improved general method for the preparation of biologically important 7 β -amino-1-oxa(thia)cephems from the corresponding 7 α -amines **1**.

Highly stereoselective conversion of 7 α -aminocephems **1** into their 7 β -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 7 α -amino-1-oxa(thia)cephems into the 7 β -amino isomers, which involved a four-step reaction sequence, *i.e.* formation of a 7 α 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 7 α -amino isomer. We suggested that this high

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

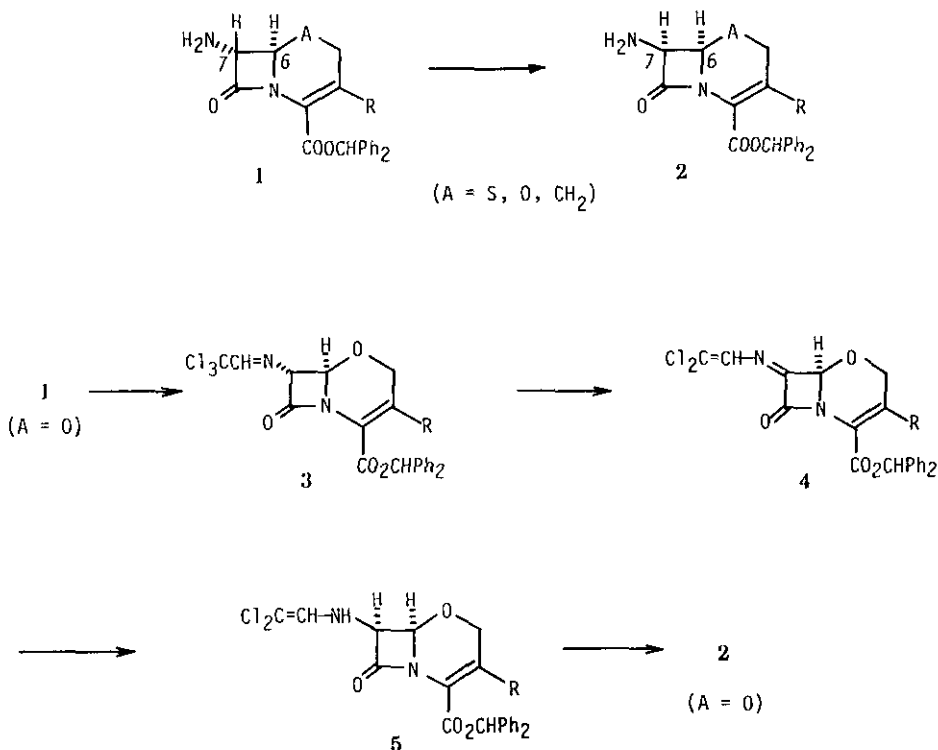


Chart 1

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 7 α - and 7 β -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 7 β -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 7 α -amino-1-oxa(thia)cephems into the 7 β -amino isomers. In this communication we wish to describe this procedure in some details.

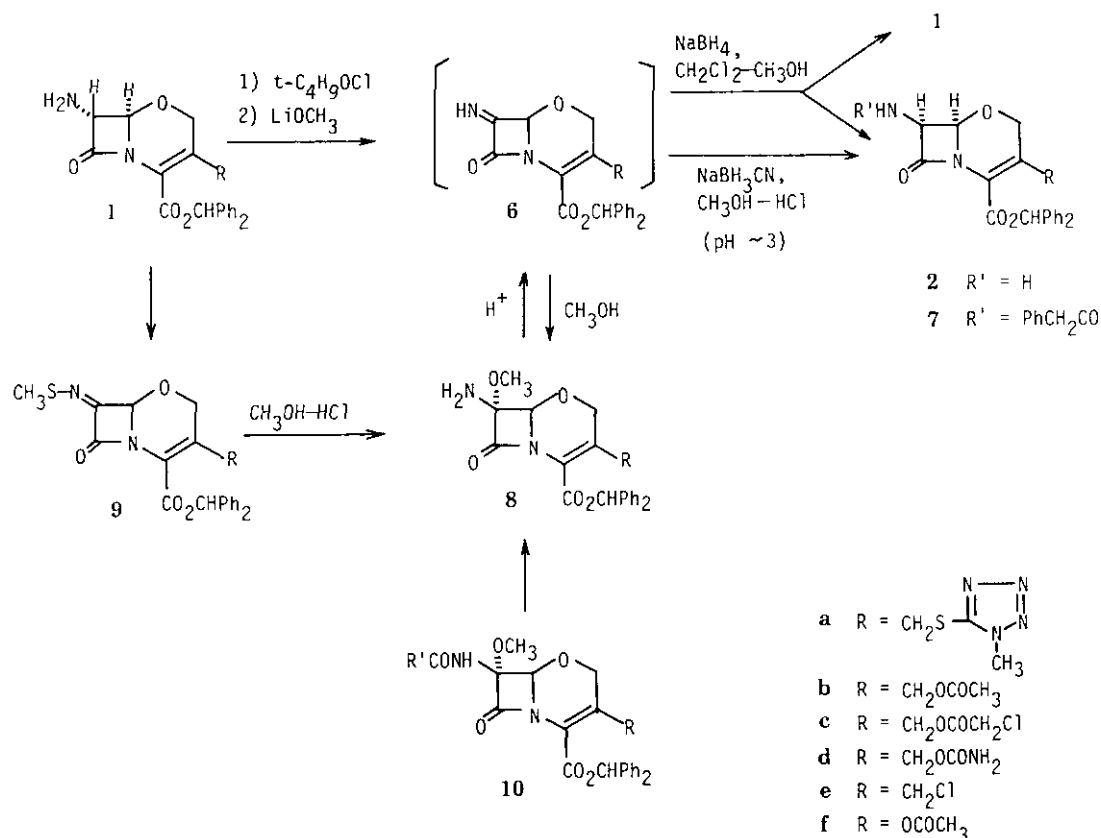
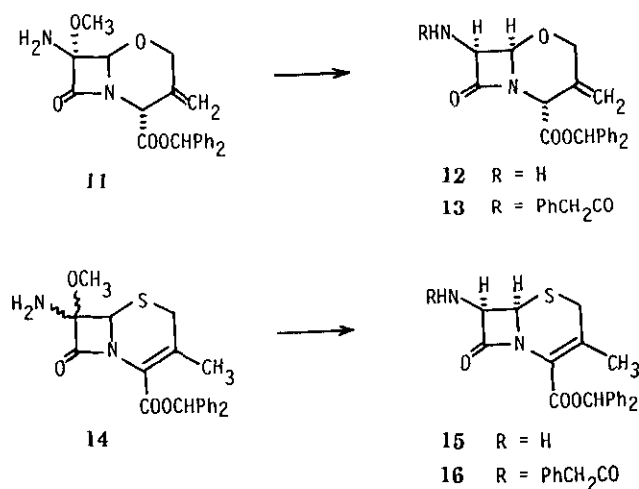


Chart 2

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, $\text{RN}=\text{CR}'\text{R}''$. In carrying out the experiment we used 7 β -amino-7 α -methoxy-1-oxacephems **8** as the substrates in place of the labile and hardly isolable 7-imino-1-oxacephems **6** which were conveniently formed as an equilibrium component⁴ when a methanol solution of the former was treated with an acid, *e.g.*, hydrogen chloride, as illustrated in Chart 2. The 7 β -amino-7 α -methoxy-1-oxacephems **8** were available from the corresponding 7 β -acylamino-1-oxacephamycin derivatives **10** by the conventional deacylation method using phosphorus pentachloride or, more conveniently, from the sulphenyl 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 7 β -benzoylamino derivative **10a** ($\text{R}' = \text{C}_6\text{H}_5$), 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



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 ($\text{H}_5\text{C}_5\text{N} \cdot \text{BH}_3$) and borane-trimethylamine complex $[(\text{CH}_3)_3\text{N} \cdot \text{BH}_3]$ were found to be useful, although the reductions with these reagents, particularly with $(\text{CH}_3)_3\text{N} \cdot \text{BH}_3$, 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 assumed⁶ 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 7 β -amines (or their phenylacetamido derivatives)

7-Methoxy- amine	Reagent	Conditions		7 β -Amine (yield, %)	Product ⁷ Phenylacetamide (yield, %)
		Time (h)	Temp. (°C)		
8a	NaBH ₃ CN	3.5	0	--	7a (90)
8a	H ₅ C ₅ N·BH ₃	5.0	0-25	2a (94)	--
8a	(CH ₃) ₃ N·BH ₃	3.0	25	--	7a (60)
8d	NaBH ₃ CN	3.0	0	--	7d (58)
11	NaBH ₃ CN	3.0	0	--	13 (96)
14	NaBH ₃ CN	2.0	0	--	16 (94)

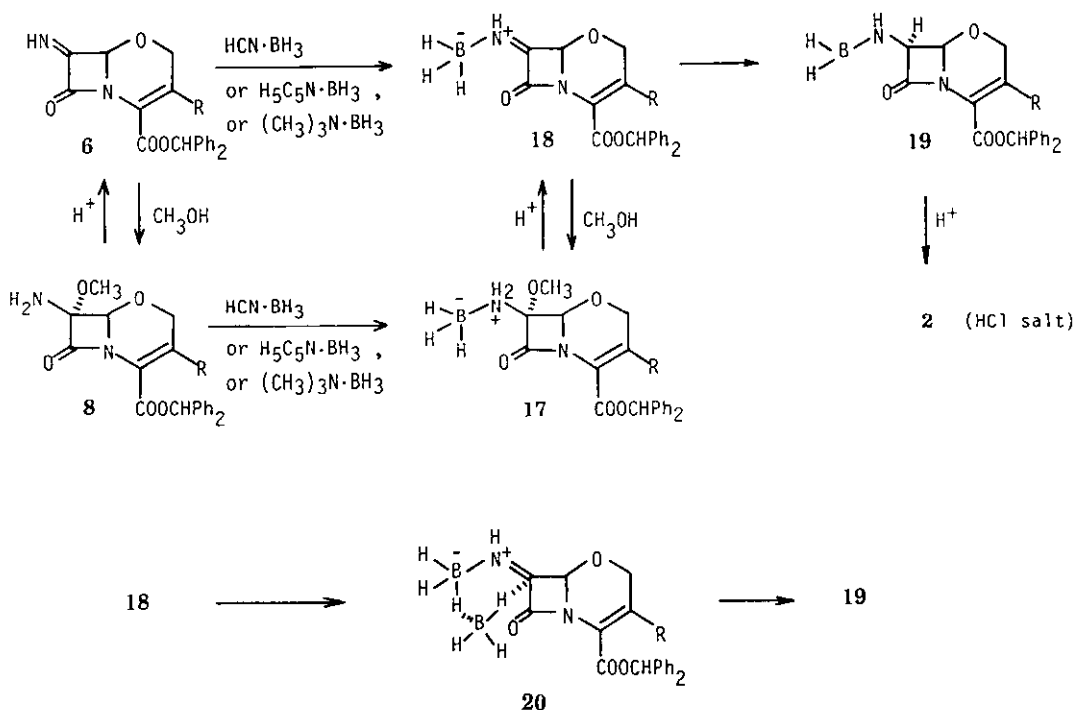
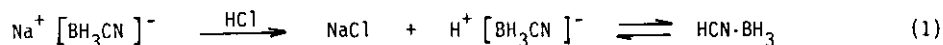


Chart 3

formula, $\text{HCN}\cdot\text{BH}_3$, via the initially formed conjugate acid, $\text{H}^+[\text{BH}_3\text{CN}]^-$ [equation (1)]. The formulation of $\text{HCN}\cdot\text{BH}_3$ is based upon an analogy to the borane-*tert*-amine complexes, such as $\text{C}_5\text{H}_5\text{N}\cdot\text{BH}_3$ and $(\text{CH}_3)_3\text{N}\cdot\text{BH}_3$, 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 reaction⁶ 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 $\text{C}_5\text{H}_5\text{N}\cdot\text{BH}_3$ or $(\text{CH}_3)_3\text{N}\cdot\text{BH}_3$ 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 $\text{H}_5\text{C}_5\text{N}\cdot\text{BH}_3$ or $(\text{CH}_3)_3\text{N}\cdot\text{BH}_3$ 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 7 α -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 7 β -aminocephems 2 from their 7 α -epimers 1. We found that dehydrogenation of 1 was most conveniently achieved via the methylsulfonylimines 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 methylsulfonylimino-1-oxacephems 9 and 3-exomethylenecepham 22 were smoothly converted into the corresponding 7 β -amines 2 (characterized as their phenylacetamido derivatives 7) and 12, respectively. The methylsulfonylimines 9 and 22 were conveniently prepared from the corresponding 7 α -amines 1 and 21 by applying the Squibb procedure⁹ involving treating the amines with methylsulfonyl 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 7 β -amino-1-oxa- or 1-thiacephems from the corresponding 7 α -isomers. We believe that this method is superior to the previously reported method² 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 $\rightarrow$ 22: To a mixture of 3-exomethylene-7 α -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 methylsulfonyl 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 7 α -amino-1-oxacephems **1** and 1-oxacephem **21** into the corresponding 7 β -amino derivatives **7** and **12** via the methylsulfenylimino derivatives **9** and **22**

7 α -Amines	Sulfenylimine ¹⁰ (yield, %)	7 β -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**.

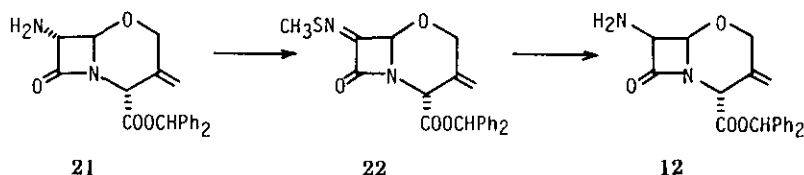
b) Crude **9e** was used for the reduction step.

c) The yield was based upon the 7 α -amine **1e**.

d) Borane-pyridine complex (BH₃·NC₅H₅) 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**.



reduced pressure and the residue was chromatographed (silica gel, benzene-ethyl acetate 9 : 1) to give 7-methylsulfenylimino-1-oxacephem **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 7 β -amino-1-oxacephem **12** (732 mg, 82%) after silica gel chromatography.

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7. Physical data of 7 β -amino derivatives are listed below. 2a: mp 165°C; ir (Nujol) 1775, 1715 cm⁻¹; nmr (CDCl₃-CD₃OD) δ 3.83 (3H, s, NCH₃), 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, Ar₂CH), 7.2-7.6 (10H, m, C₆H₅). 7a: mp 197°C; ir (Nujol) 3320, 1785, 1705, 1653 cm⁻¹; nmr (CDCl₃) δ 3.60 (2H, s, ArCH₂), 3.76 (3H, s, NCH₃), 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, Ar₂CH), 7.15-7.65 (15H, m, C₆H₅). 7d: Ir (CHCl₃) 3500, 3420, 1785, 1720, 1675 cm⁻¹; nmr (CDCl₃) δ 3.58 (2H, s, ArCH₂), 4.29 (2H, s, H-2), 4.75-5.18 (5H, m, H-3', H-6, CONH₂), 5.65 (1H, dd, J = 10, 4 Hz, H-7), 6.54 (1H, d, J = 10 Hz, CONH), 6.85 (1H, s, Ar₂CH), 7.15-7.60 (15H, m, C₆H₅). 13: Ir (CHCl₃) 3400, 1770, 1733, 1673 cm⁻¹; nmr (CDCl₃) δ 3.55 (2H, s, ArCH₂), 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=CH₂), 5.52 (1H, dd, J = 10, 4 Hz, H-7), 6.22 (1H, d, J = 10 Hz, CONH), 6.85 (1H, s, Ar₂CH), 7.20-7.40 (15H, m, C₆H₅). 16: Ir (Nujol) 3250, 1760, 1710, 1650 cm⁻¹; nmr (CD₃SOCD₃-CD₃OD) δ 2.03 (3H, s, CH₃), 3.40, 3.57 (2H, ABq, J = 22.5 Hz, H-2), 3.57 (2H, s, ArCH₂), 5.06 (1H, d, J = 4 Hz, H-6), 5.68 (1H, dd, J = 10, 4 Hz, H-7), 6.90 (1H, s, Ar₂CH), 7.2-7.6 (15H, m, C₆H₅), 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 iminium ion (H instead of H₃B⁺ in 18 in Chart 3) which is then attacked by BH₃CN⁻ 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 methylsulfonylimino derivatives are listed below. 9b: Ir (CHCl₃) 1780, 1730 cm⁻¹; nmr (CDCl₃) δ 1.99 (3H, s, COCH₃), 2.86 (3H, s, SCH₃), 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, Ar₂CH), 7.20-7.80 (10 H, m, C₆H₅). 9c: Ir (CHCl₃) 1780, 1720 cm⁻¹; nmr (CDCl₃) δ 2.86 (3H, s, SCH₃), 3.96 (2H, s, CH₂Cl), 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, Ar₂CH), 7.30-7.70 (10H, m, C₆H₅). 9f: mp 142°C; ir (CHCl₃) 1775, 1725, 1635 cm⁻¹; nmr (CDCl₃) δ 2.03 (3H, s, COCH₃), 2.85 (3H, s, SCH₃), 4.37 (2H, s, H-2), 5.42 (1H, brs, H-6), 6.92 (1H, s, Ar₂CH), 7.20-7.60 (10H, m, C₆H₅). 22: Ir (CHCl₃) 1775, 1740 cm⁻¹; nmr (CDCl₃) δ 2.76 (3H, s, SCH₃), 4.24 (2H, s, H-2), 5.72, 5.79, 5.82 (3H, each s, H-3, H-4, -C=CH₂), 5.67 (1H, brs, H-6), 6.88 (1H, s, Ar₂CH), 7.20-7.40 (10H, m, C₆H₅).
11. Physical data of 7β-amino derivatives are listed below. 7b: Ir (CHCl₃) 3410, 1790, 1730, 1680 cm⁻¹; nmr (CDCl₃) δ 1.96 (3H, s, COCH₃), 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, CONH), 7.20-7.60 (15 H, m, C₆H₅). 7c: Ir (CHCl₃) 1785, 1715, 1670 cm⁻¹; nmr (CDCl₃) δ 3.62 (2H, s, ArCH₂), 3.93 (2H, s, COCH₂Cl), 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, CONH), 6.88 (1H, s, Ar₂CH), 7.20-7.60 (15H, m, C₆H₅). 7e: Ir (CHCl₃) 3400, 1790, 1720, 1670 cm⁻¹; nmr (CDCl₃) δ 3.60 (2H, s, ArCH₂), 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, CONH), 6.88 (1H, s, Ar₂CH), 7.20-7.50 (15 H, m, C₆H₅). 7f: Ir (CHCl₃) 3420, 1800, 1726, 1685 cm⁻¹; nmr (CDCl₃) δ 1.99 (3H, s, COCH₃), 3.57 (2H, s, ArCH₂), 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, CONH), 6.88 (1H, s, Ar₂CH), 7.20-7.50 (15 H, m, C₆H₅). 12: Ir (CHCl₃) 3380, 1760, 1732 cm⁻¹; nmr (CDCl₃) δ 1.66 (2H, brs, NH₂), 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=CH₂), 6.86 (1H, s, Ar₂CH), 7.20-7.40 (10 H, m, C₆H₅).

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