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SYNTHETIC STUDIES ON CARBAPENEM ANTIBIOTICS FROM PENICILLINS. IV[1]. STEREOSELECTIVE KINETIC PROTONATION OF A CHIRAL AZETIDINONE ENOLATE

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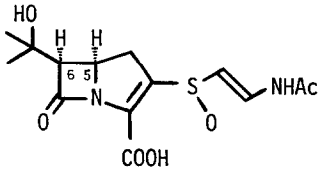
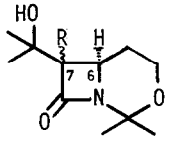
Summary: A stereoselective kinetic protonation of the azetidinone enolate B was studied and an efficient synthesis of 2(cis) was achieved via aldol reaction of 5 with acetone followed by the kinetic protonation with Ph_3SnH as proton source.

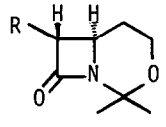
In conjunction with our work on the synthesis of chiral carbapenem antibiotics from penicillins[1], our attention has been focused on the stereoselective synthesis of the chiral 6,7-cis-azetidinone 2(cis) which is a key intermediate for the optically active 5,6-cis-carbapenem antibiotics represented by carpetimycin A (1)[2]. Our approach that we reported recently[1b] was based on the n-Bu_3SnH radical reduction of isocyanoazetidinone 4, in which the preferential formation of 2(cis) was attributed to the approach of the bulky n-Bu_3SnH from the α-side of the radical intermediate A owing to considerable steric interferences of the C-6 ß-substituent of the substrate. This argument prompted us further to investigate a kinetic protonation of the azetidinone enolate B which could be derived from 2[1b] by base treatment. It



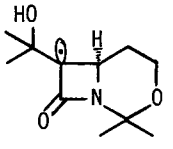
1



2 R = H
3 R = D
4 R = NC



5 R = H
6 R = NC



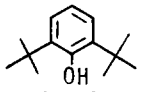
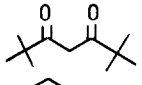
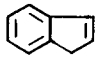
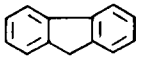
A

B

has been felt that proton sources in such kinetic protonation should be not only bulky but soft with appropriate basicities (pka 10∿25), because the protonation should occur at the C-7 carbon instead of the enolate oxygen in B[3]. We wish to report here a study for the kinetic protonation of B using some proton sources for transformation of 2(trans) to 2(cis) and an efficient synthesis of 2(cis) by aldol reaction of 5 with acetone followed by the kinetic protonation.

For investigation of the kinetic protonation of B, it was necessary first of all to estimate the yield of B from 2. For this purpose, we examined deuterization of B starting from pure 2(cis) and 2(trans) and the incorporation extents of deuterium were determined as follows. The compounds 2(cis) and 2(trans) were treated with *n*-BuLi (4 equiv, THF, -78°C, 1.5 h) to lead B and followed by quenching with CD_3COOD (8 equiv, -78°C). The ^1H NMR spectra of the products 3 showed that the incorporations of deuterium into C-7 of 3 were 70% from 2(cis) and 52% from 2(trans)[4], respectively. Therefore, we initially chose 2(cis) as the precursor for examinations on the kinetic protonation of B.

Table Kinetic Protonation of the Azetidinone Enolate B Derived from 2(cis)

Entry	Proton Source	Products 2		Kinetic Protonation
		Yield	Ratio(cis/trans)	Ratio(cis/trans)[a]
1	CH_3COOH	99%	0.82	0.27[b]
2		94%	0.88	0.32
3		98%	1.06	0.44
4		99%	1.63	0.84
5		94%	1.86	1.00
6	Ph_3SiH	61%[c]	1.38	0.67
7	Ph_3SnH	96%	4.98	3.19

[a]Since the azetidinone enolate B was generated in 70% yield from 2(cis), ratio of the kinetic protonation was defined as:

ratio(cis/trans) = product's ratio - (product's ratio + 1) X 0.3

[b]A 0.38 ratio was obtained starting from 2(trans).

[c]Because the protonation of Ph_3SiH was hard to occur owing to its high basicity[5], a competitive ring opening reaction of B[4] proceeded, when the temperature was raised to -20°C∿0°C, to give the byproduct ii (34% yield)[4].

The typical procedure for deprotonation and successive protonation was as follows. Treatment of 2(cis) with *n*-BuLi as described above, followed by slowly adding a cooled solution of a proton source (8 equiv, -78°C) in THF, afforded, after quenching with CH_3COOH (8 equiv, r.t.) and workup in the usual manner, a mixture of 2(cis) and 2(trans), whose ratio was estimated by measurement of the ^1H NMR spectrum and the ratio of the kinetic protonation to B was calculated as shown in the Table(see footnote). In the protonation with CH_3COOH(Entry 1), the major product was 2(trans) (cis/trans=0.27) and a similar ratio (cis/trans=0.32) was obtained in the protonation with 2,6-di-(*t*-butyl)phenol (Entry 2). The preferential formation of the trans product by using such hard O-H protons might be envisioned as a result of protonation at the enolate oxygen in B and successive reversion to the thermodynamically stable 2(trans). It was found, on the contrary, that protonation with soft protons was effectual for the formation of 2(cis) to give ratios of cis/trans = 0.67∿3.19(Entry 4∿7). Especially, when Ph_3SnH was used as the proton source, the most desirable result was obtained (cis/trans=3.19) (Entry 7). This result indicates that Ph_3SnH attacked on the C-7 carbanion in B from the α-face (owing to a steric influence of the 6ß-CH_2 group), the stereochemistry being thus controlled to the advantage of 2(cis).

We then turned to the transformation of 2(trans) to 2(cis). Treatment of 2(trans) with *n*-BuLi as described above to lead B, followed by protonation with Ph_3SnH in the same way, yielded 2 in a 0.68 ratio of cis/trans(96% yield). Based on the 52% yield of B from 2(trans) as shown above, the ratio of 2(cis)/2(trans) formed by the kinetic protonation is estimated as 3.51[6]. The isolation of 2(cis) from the mixture by column chromatography (silica gel) eluting with acetone/CH_2Cl_2 was 37% yield.

For a more practical usage of this method for the synthesis of 5,6-cis-carbapenems, we finally explored the application to a one-pot synthesis of 2(cis) from 5 which was obtained by reduction of 6[1b] with *n*-Bu_3SnH (AIBN, benzene reflux, 88%). After treatment of 5 with *n*-BuLi (1.05 equiv, THF, -78°C, 0.2 h) followed by addition of acetone (1.05 equiv, -78°C, 0.5 h)[7], the reaction mixture was treated with an additional *n*-BuLi (3 equiv, -78°C, 1.5 h) and successively quenched with Ph_3SnH in the same manner. The product ratio of 2(cis) to 2(trans) was 0.68 (98%) and the isolated yield of 2(cis) was 37%[8].

In conclusion, the present methodology provides a new guidance for the stereoselective synthesis of 5,6-cis-carbapenem antibiotics and could further be applicable for the synthesis of other natural products.

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1. (a) Part II: Hirai, H.; Sawada, K.; Aratani, M.; Hashimoto, M. Tetrahedron Lett., 1984, 25, 5075. (b) Part III: Aratani, M.; Hirai, H.; Sawada, K.; Yamada, A.; Hashimoto, M. ibid., in press.
2. (a) Nakayama, M.; Iwasaki, A.; Kimura, S.; Mizoguchi, T.; Tanabe, S.; Murakami, A.; Watanabe, I.; Okuchi, M.; Itoh, H.; Saino, Y.; Kobayashi, F.; Mori, T. J. Antibiot., 1980, 33, 1388. (b) Imada, A.; Nozaki, Y.; Kintaka. K.; Okanogi, K.; Kitano, K.; Harada, S. ibid., 1980, 33, 1477. (c) Okanogi, K.; Harada, S.; Shinagawa, S.; Imada, A.; Kuno, M. ibid., 1982, 35, 963. (d) Kakayama, M.; Kimura, S.; Mizoguchi, T.; Tanabe, S.; Iwasaki, A.; Murakami, A.; Okuchi, M.; Itoh, H. 1983, 36, 943.
3. For a discussion on the kinetic protonation, see: Takano, S.; Uchida, W.; Hatakeyama, S.; Ogasawara, K. Chemistry Lett., 1982, 733.
4. The 52% yield of 3 from 2(trans) was best after all examinations under various conditions (base: *n*,*s*,*t*-BuLi, MeLi, *n*-BuLi-*t*-BuOK, *n*-BuLi-NaH, NaH; additive: HMPA, TMEDA in THF; temperature: -78°C, -78°C∿-20°C, -78°C∿0°C for the deprotonation). At the elevated temperatures (-20°C∿0°C), ii was obtained as a byproduct probably via migration of the C-2 methyl proton to C-7 as depicted in i.

i ii

5. Gilman, H.; Marrs, O.L.; Trepka, W. J.; Diehl, J. W. J. Org. Chem., 1962, 27, 1260.
6. Since the azetidinone enolate B was generated in 52% yield from 2(trans), the ratio of the kinetic protonation was defined as:

$$\text{ratio(cis/trans)} = \frac{\text{product's ratio(cis/trans)}}{1 - (\text{product's Ratio(cis/trans)} + 1) \times 0.48}$$

7. For the aldol reaction of 5 with acetone, see: Natsugari, H.; Matsushita, Y.; Tamura, N.; Yoshioka, K.; Kondo, M.; Okanogi, K.; Kuno, M.; Ochiai, M. J. Antibiot., 1983, 36, 855.
8. For the synthesis of 5,6-cis-carbapenems from 2(cis), see ref. 1b.

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