That is, the regioselectivity may be rationalized as due to the ease of the deprotonation from **4**, since the stronger the acidity of the methyl or methylene hydrogen, the easier the deprotonation. In support of this, Kimura et al. have found that in the anodic oxidation of cyanomethyl sulfides in methanol, the electron-withdrawing cyano group facilitates deprotonation and methoxylation at their α-positions.[19] In addition, the stability of the radical intermediates **5** and **6** would aslo affect this regioselectivity. Most recently, Kubota et al. have found that the anodic oxidation of 3-hydroxy-2-(trifluoromethyl)propionic acid generated radicals α to the trifluoromethyl group, leading to their dimer almost quantitatively.[20] Their results and ours may suggest that the stabilizaion of the radical intermediate **5** by a sort of the captodative effect[21] also presumably contributes to this high regioselectivity.

In order to demonstrate the synthetic utility of the α-methoxylated products **3**, we generated α-trifluoromethylated iminium cations, which we trapped with various carbon nucleophiles. For example, treatment of **3b** with a Lewis acid, such as $TiCl_4$, in the presence of a silyl enol either efficiently provided a heterocyclic product **9** bearing a trifluoromethyl group together with an amino ketone **10** as shown in Scheme V.[22] A cyano group was similarly introduced to the α-position toward the trifluoromethyl group of **3b** to give α-amino nitrile **11** in reasonable yield (Scheme V).[23]

Thus, the α-methoxyanilines **3** were found to be highly useful building blocks for the construction of a carbon–carbon bond α to the trifluoromethyl group.

Acknowledgment. We thank Tsuyoshi Takiguchi and Yasushi Fujita for measurement of the anodic oxidation potentials of (trifluoroethyl)amines, Prof. Tomoya Kitazume of Tokyo Institute of Technology for obtaining ^{19}F NMR spectra, and Ajinomoto Co., Inc., Central Research Laboratories, and Dr. Toshio Kubota of Ibaragi University for measurement of the high-resolution mass spectra.

Registry No. 2a, 55204-33-6; **2b**, 55204-36-9; **2c**, 110972-14-0; **3a**, 110972-15-1; **3b**, 110972-16-2; **3c**, 110972-17-3; **9**, 110972-18-4; **10**, 110972-19-5; **11**, 110972-20-8; $Me_3SiOC{=}CHCH_2CH_2CH_2CH_2$, 6651-36-1; Me_3SiCN, 7677-24-9.

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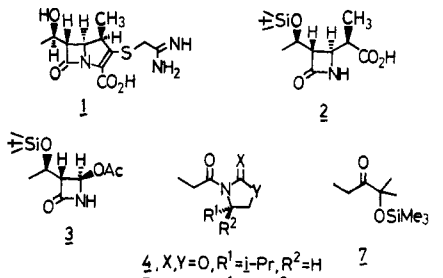
A New Approach to the Chiral Synthesis of the 1-β-Methylcarbapenem Key Precursor Using an Achiral Ketone Sn(II) Enolate

Summary: A highly stereoselective synthesis of the chiral 1-β-methylcarbapenem key precursor has been accomplished by the aldol-type reaction of the chiral 4-acetoxyazetidinone with a tin(II) enolate generated from 2-methyl-2-siloxy-3-pentanone.

Sir: Since the Merck group reported the enhanced chemical and metabolic stability of the 1-β-methylcarbapenem antibiotics such as **1**,[1] the chiral synthesis of the 1-β-methylcarbapenem key precursor (**2**) has been the subject of considerable synthetic activities.[2] The most extensively studied route to precursor **2** is based on the stereocontrolled aldol-type reaction of the readily available (+)-4-acetoxy-2-azetidinone (**3**)[3] with an appropriate equivalent



to the enolate of propionic acid, where the choice of the enolate equivalent is the key to success. Recently, efficient

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(20) Kubota, T.; Aoyagi, R.; Sando, H.; Kawasumi, M.; Tanaka, T. *Chem. Lett.* **1987**, 1435.

(21) Viehe, H. G.; Janousek, Z.; Merenyi, R. *Acc. Chem. Res.* **1985**, *18*, 148.

(22) The reaction was carried out as follows. To a solution of 0.5 mmol of *N*-ethyl-*N*-(1-methoxy-2,2,2-trifluoroethyl)aniline (**3b**) in 0.5 mL of anhydrous dichloromethane was added dropwise a solution of 0.65 mmol of $TiCl_4$ in 0.77 mL at ca. −78 °C. After 5 min of stirring, a solution of 0.65 mmol of 2-cyclohexenyl trimethylsilyl ether in 0.5 mL of dichloromethane was added dropwise, and then the resulting solution was stirred for 0.5 h at the same temperature. To the reaction mixture, saturated aqueous potassium carbonate was added. The solution was repeatedly extracted with dichloromethane, washed with water, and then dried over anhydrous sodium sulfate. The extracts were concentrated under reduced pressure, and the remaining oil was chromatographed on silica gel (hexane–AcOEt, 20:1) to provide **9** and **10** as the first and second components, respectively. **1-Ethyl-2-(trifluoromethyl)-3,4-butano-1,2-dihydroquinoline (9)**: ^1H NMR ($CDCl_3$) δ 1.20 (t, 3 H, CH_3, J_{H-H} = 7 Hz), 1.6–2.7 (m, 8 H, CH_2CH_2), 3.22, 2.53 (q, 2 H, CH_3CH_2, J_{H-H} = 7 Hz), 4.03 (q, 1 H, CF_3CH, J_{H-F} = 7 Hz), 6.5–7.2 (m, 4 H, C_6H_4); ^{19}F NMR ($CDCl_3$, ext. CF_3CO_2H) δ −4.6 (d); MS, *m/e* 281 (M^+), 212 ($M^+ - CF_3$), 184 ($M^+ - CF_3 - C_2H_4$), 156 ($M^+ - CF_3 - 2C_2H_4$); calcd for $C_{16}H_{18}F_3N$ *m/e* 281.1391, found *m/e* 281.1296. ***N*-Ethyl-*N*-[1-(2-oxocyclohexyl)-2,2,2-trifluoroethyl]alanine (10)**: ^1H NMR ($CDCl_3$) δ 1.13, 1.20 (dt, 3 H, CH_3, J_{H-H} = 7 Hz), 1.0–2.7 (m, 8 H, CH_2), 3.22 (q, 1 H, CHCO), 3.45 (q, 2 H, CH_3CH_2, J_{H-H} = 7 Hz), 5.13 (quint, 1 H, CF_3CH, J_{H-F} = 9 Hz), 6.7–7.4 (m, 5 H, C_6H_5); ^{19}F NMR ($CDCl_3$, ext. CF_3CO_2H) δ −8.5 (d), −9.9 (d); IR 1730 (C=O), 1620, 1605 cm^{-1} (C=C); MS, *m/e* 299 (M^+), 230 ($M^+ - CF_3$), 202 ($M^+ - CF_3 - C_2H_4$), 174 ($M^+ - CF_3 - 2C_2H_4$), 120 (PhN^+Et), 77 (Ph^+); calcd for $C_{16}H_{20}F_3NO$ *m/e* 299.1497, found *m/e* 299.1502.

(23) The α-amino nitrile **11** was synthesized in the manner similar to the preparation of **9** and **10**, however, the reaction was not optimized. ***N*-(1-Cyano-2,2,2-trifluoroethyl)-*N*-ethylaniline (11)**: ^1H NMR ($CDCl_3$) δ 1.10 (t, 3 H, CH_3, J_{H-H} = 7 Hz), 3.43 (q, 2 H, CH_3CH_2, J_{H-H} = 7 Hz), 4.83 (q, 1 H, CF_3CH, J_{H-H} = 7 Hz), 6.7–7.4 (m, 5 H, C_6H_5); ^{19}F NMR (CCl_3, ext. CF_3CO_2H), δ −6.3 (d); MS, *m/e* 228 (M^+), 213 (M^+ – Me), 159 ($M^+ - CF_3$), 105 ($PhNCH_2^+$), 77 (Ph^+); calcd for $C_{11}H_{11}F_3N_2$ *m/e* 228.2165, found *m/e* 228.2186.

(1) Shih, D. H.; Baker, F.; Cama, L.; Christensen, B. G. *Heterocycles* **1984**, *21*, 29.

(2) (a) Fuentes, L. M.; Shinkai, I.; Salzmann, T. N. *J. am. Chem. Soc.* **1986**, *108*, 4675. (b) Nagao, Y.; Kumagai, T.; Tamai, S.; Abe, T.; Kuramoto, Y.; Taga, T.; Aoyagi, S.; Nagase, Y.; Ochiai, M.; Inoue, Y.; Fujita, E. *Ibid.* **1986**, *108*, 4673. (c) Dëziel, R.; Favreau, D. *Tetrahedron Lett.* **1986**, *27*, 5687. (d) Kim, C. U.; Luh, B.; Partyka, R. A. *Ibid.* **1987**, *28*, 507. (e) Shibata, T.; Iino, K.; Tanaka, T.; Hashimoto, T.; Kameyama, Y.; Sugimura, Y. *Ibid.* **1985**, *26*, 4739. (f) Chiba, T.; Nagatsuma, M.; Nakai, T. *Chem. Lett.* **1985**, 1343. (g) Iimori, T.; Shibasaki, M. *Tetrahedron Lett.* **1986**, *27*, 2149. (h) Prasad, J. S.; Liebeskind, L. S. *Ibid.* **1987**, *28*, 1857. (i) Hatanaka, M. *Ibid.* **1987**, *28*, 83.

(3) (a) Review (in Japanese) on the synthesis of (+)-**3** from (*R*)-β-hydroxybutyric acid derivatives: Nakai, T.; Chiba, T. *Farumashia* **1986**, *22*, 611. (b) Chiba, T.; Nakai, T. *Tetrahedron Lett.* **1985**, *26*, 4647 and references therein. (c) Leanza, W. J.; DiNinno, F.; Muthard, D. A.; Wilkening, R. R.; Wildonger, K. J.; Ratcliff, R. W.; Christensen, B. G. *Tetrahedron* **1983**, *39*, 2505 and references therein. (c) Shiozaki, M.; Ishida, N.; Maruyama, H.; Hiraoka, T. *Ibid.* **1983**, *39*, 2399 and references therein. (d) Reider, P. J.; Grabowski, E. J. J. *Tetrahedron Lett.* **1982**, *23*, 2293 and references therein. (e) Hanessian, S.; Bedeschi, A.; Battistini, C.; Mongelli, N. *J. Am. Chem. Soc.* **1985**, *107*, 1438 and references therein.

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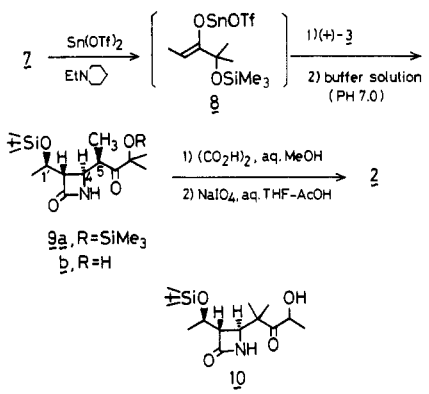
Scheme I

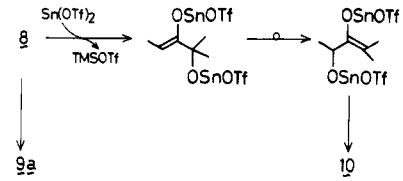


syntheses of **2** have been accomplished by highly diastereoselective aldol-type reactions which employ a boron enolate of the *chiral* oxazolidone **4** (coupled with zinc bromide)[2a] and tin(II) enolates of the *chiral* thiazolidinethione **5**[2b] and the *achiral* oxazolidinethione **6**.[2c] We now report that the utilization of the tin(II) enolate of the simple *achiral* ketone **7**[4] provides a remarkably high diastereoselectivity to afford the key precursor **2** in ≥95% diastereomeric purity.

Scheme I depicts the overall transformation we have now developed. Tin(II) enolate **8** was generated by treatment of ketone **7** (2.5 equiv based on (+)-**3** used) with tin triflate[5] (2.0 equiv) and *N*-ethylpiperidine (2.0 equiv) in dichloromethane at −70 °C, and to this solution was added a dichloromethane solution of the azetidinone (+)-**3** at that temperature. After being stirred at room temperature for 2 h, the reaction mixture was treated with a phosphate buffer solution (pH 7.0). Usual workup followed by column chromatography afforded the adduct **9a** (R = $SiMe_3$)[6] in 90% isolated yield, along with a small amount (4% yield) of the unexpected adduct **10**.[7] NMR analysis (500 MHz) of the unpurified products revealed that the diastereomeric ratio (β/α) for **9a** was 95/5.[8,9] The adduct **9a** was then subjected to desilylation followed by oxidative cleavage to afford the desired precursor **2** with ≥95% β-selectivity[10] in 72% overall yield from **9a**.

The synthetic operations described above deserve special comment. (1) Surprisingly enough, the stoichiometry of ketone to tin triflate (and amine) was found to play a key factor in determining the product composition. While the use of an excess of ketone **7** provides almost exclusively the desired adduct **9a** as described above, the use of equimolar amounts (2.5 equiv) of ketone **7**, $Sn(OTf)_2$, and the amine resulted in a considerably increased yield (40%) of the unexpected adduct **10**, together with 60% yield of **9a** (β/α = 94/6). We suggest that the enolate-to-enolate isomerization depicted below might be responsible for the formation of the unusual product **10**. (2) The specific

Enolate Isomerization



structure of ketone **7** is indispensable for the aldol-type reaction concerned.[11] Attempted reactions using 2-siloxy-3-pentanone[12] in place of ketone **7** totally failed under similar conditions, giving no adducts at all. (3) More conveniently, the tedious desilylation step in the above-mentioned procedure can be omited by treatment of the resulting reaction mixture with aqueous ammonium chloride solution instead of the buffer solution, thereby permitting direct isolation of the desilylated adduct **9b** (R = H). Thus, the synthesis of **2** from (+)-**3** can be accomplished by the two-step operation requiring no purification of the intermediate.

In summary, we have now developed a convenient new method for preparing the 1-β-methylcarbapenem key precursor. The structural simplicity of the enolate precursor, coupled with the easy availability of (+)-**3**, makes the present approach an attractive method of choice for a relatively large scale synthesis of the key precursor **2**. Further improvement of the method outlined here is in progress.

Acknowledgment. We thank Dr. T. Takaya and Mr. T. Chiba of Fujisawa Pharmaceutical Co. for their valuable discussions.

(4) Heathcock and co-workers have reported that the (*Z*)-lithium enolate of this ketone exhibits exceptionally high erythro selectivity in the aldol reactions: Heathcock, C. H.; Buse, C. T.; Kleschick, W. A.; Pirrung, M. C.; Sohn, J. E.; Lamp, J. *J. Org. Chem.* **1980**, *45*, 1066.

(5) For the utilization of $Sn(OTf)_2$ for generating tin(II) enolates, see: Mukaiyama, T.; Iwasawa, N.; Stevens, R. W.; Haga, T. *Tetrahedron* **1984**, 40, 1381 and references cited therein.

(6) Mp 162 °C; IR ($CHCl_3$) 3410, 1750, 1705 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ −0.006 (s, 3 H), 0.004 (s, 3 H), 0.125 (s, 9 H), 0.806 (s, 9 H), 1.083 (d, J = 7.02 Hz, 3 H), 1.111 (d, J = 6.4 Hz, 3 H), 1.261 (s, 3 H), 1.307 (s, 3 H), 2.834 (dd, J = 1.8 and 4.27 Hz, 1 H), 3.495 (dq, J = 5.19 and 7.02 Hz, 1 H), 3.746 (dd, J = 1.84 and 5.19 Hz, 1 H), 4.099 (dq, J = 6.41 and 4.27 Hz, 1 H), 5.817 (br s, 1 H); $[\alpha]^{17}_D$ −3.8° (*c* 1.0, $CHCl_3$) for the 94:6 mixture of **9a** and its 1α-epimer.

(7) IR ($CHCl_3$) 3500, 3400, 1760, 1700 cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$) δ 0.08 (s, 6 H), 0.77 (s, 9 H), 1.08 (s, 3 H), 1.13 (d, J = 6.0 Hz, 3 H), 1.19 (s, 3 H), 1.25 (d, J = 7.5 Hz, 3 H), 2.77 (dd, J = 2.0 and 6.0 Hz, 1 H), 3.82 (d, J = 2.0 Hz, 1 H), 4.10 (dq, J = 6.0 and 6.0 Hz, 1 H), 4.50 (q, J = 7.5 Hz, 1 H), 6.80 (br s, 1 H).

(8) The two stereoisomers, **9a** and its 1α-epimer, are clearly distinguishable by 500-MHz NMR. Selected δ values for **9a**/its 1α-epimer are as follows: 1.083/1.130 (d, 5-CH_3), 1.111/1.190 (d, 1'-CH_3), 2.834/2.706 (dd, 3-H), 3.746/3.695 (dd, 4-H).

(9) This high β-diastereoselectivity can be rationalized by essentially the same cyclic transition state as advanced for explaining the comparably high β-selectivity observed with the boron[2a] and tin(II) enolates.[2b]

(10) Determined by the ^1H NMR spectrum which is in accord with the reported values.[1]

(11) It is noteworthy that a similar reaction employing the tin enolate of 2,2-dimethyl-3-pentanone was found to afford only a low yield (≤10%) of the corresponding adduct, although the diastereoselectivity was quite high (≥95% β). Another notable finding is that an attempted reaction of the silyl enol ether of ketone **7** with (+)-**3** in the presence of zinc iodide did not afford any adducts at all.

(12) This ketone is of special interest because both the tin enolates generated directly from this ketone and via the enolate-to-enolate isomerization could give rise to the identical adduct.

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Chelate Selectivity in Chelation-Controlled Allylations. A New Synthesis of Castanospermine and Other Bioactive Indolizidine Alkaloids

Summary: An efficient synthesis of polyhydroxylated indolizidine alkaloids relies on new heteroatom-selective Sakurai reactions with $TiCl_4$.

Sir: Synthetic carbohydrate chemistry has, in the past decade, enjoyed a renaissance as a critical testing ground for evaluating new methods of relative and absolute ste-

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