A new diastereoselective synthesis of a 1β-methylcarbapenem intermediate

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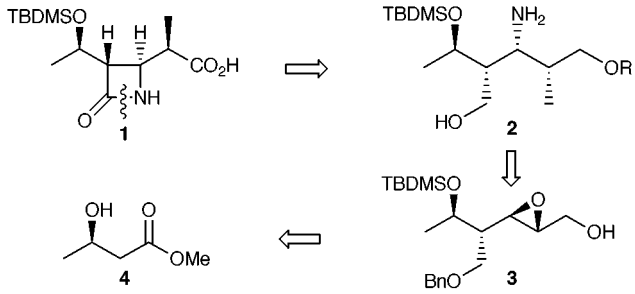
A 1β-methylcarbapenem key intermediate is synthesized from methyl (*R*)-3-hydroxybutyrate *via* the diastereoselective alkylation and regioselective cuprate ring opening of a chiral epoxide which is readily prepared from Sharpless asymmetric epoxidation of the corresponding allylic alcohol.

The discovery that 1β-methylcarbapenem has potent and broad-spectrum antibacterial activitiy as well as enhanced metabolic and chemical stability[1] has prompted many synthetic organic chemists to develop efficient methods for the stereoselective synthesis of the key 1β-methyl intermediate **1**, and recent reviews describe impressive progress in this area.[2, 3]

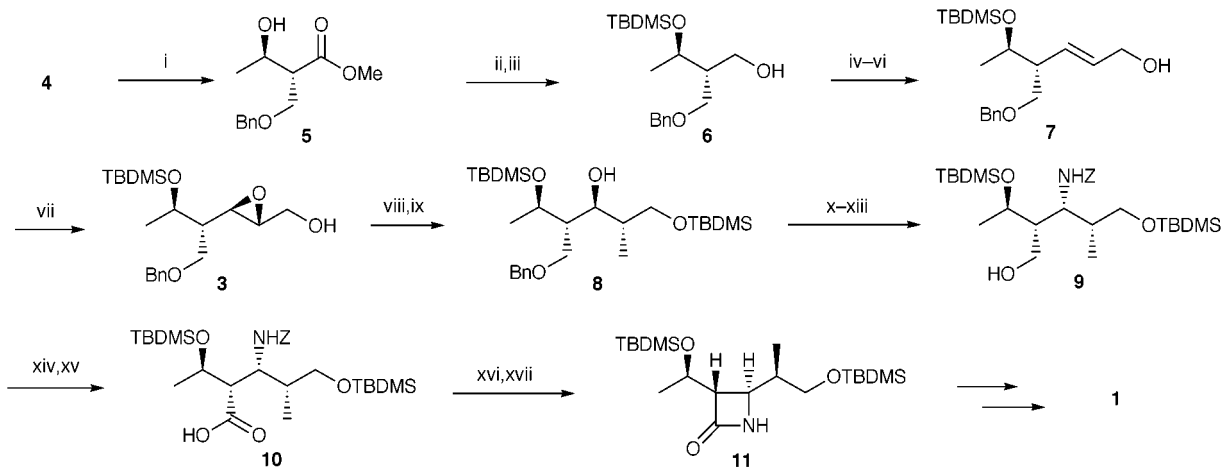
Our approach to the enantioselective synthesis of **1** relies on regioselective ring opening of chiral epoxy alcohol **3**, which is readily available from Sharpless asymmetric epoxidation of the allylic alcohol (Scheme 1). This allylic alcohol **7**, containing two stereocenters which are requisite for key intermediate **1**, could be easily obtained from diastereoselective alkylation of methyl (*R*)-3-hydroxybutyrate **4** followed by a short transformation.



Scheme 1

Thus, methyl ester **4**, available in high enantiomeric purity, was converted into the allylic alcohol **7** as shown in Scheme 2. To this end, β-hydroxy ester **4** was alkylated with benzyloxymethyl chloride (BOMCl). Generally, alkylation of the dianions of such β-hydroxy esters has been shown to yield products of high diastereomeric excess with predictable stereoselectivity, but in this case alkylation with BOMCl afforded the benzyl ether with moderate stereoselectivity (*ca.* 10::1) and low conversion yield (*ca.* 50%).[4–6] Fortunately, there was a dramatic improvement both in conversion yield and diastereomeric ratio (70% and 35:1) when we added HMPA as an additive.[7] The secondary alcohol of the resulting benzyl ether **6** was protected as an TBDMS ether in high yield and the ester was subsequently reduced to the corresponding alcohol **6** with DIBAL-H at −78 °C. Swern oxidation of **6** afforded the aldehyde, which without purification was subjected to a Horner olefination with triethyl phosphonoacetate under the conditions developed by Masamune and Roush.[8] to give the α,β-unsaturated ester with complete *E*-selectivity. Reduction of the *E*-unsaturated ester using DIBAL-H at −78 °C produced the allylic alcohol **7**. The epoxidation of this allylic alcohol under Sharpless conditions employing D-(−)-diisopropyl tartrate as stereodirecting ligand gave rise to the epoxide **3** with excellent diastereoselectivity (15:1). The stage was now set to introduce the fourth chiral center in **3** and for this we made use of the ubiquitous high order cuprate protocol; the highly regioselective opening of the epoxide with $Me_2Cu(CN)Li_2$ gave the 1,3-diol. The primary hydroxy group of the resulting diol was selectively protected as a TBDMS ether to give **8**.

The conversion of **8** to **9** was accomplished by a four step sequence. Mesylation of the secondary alcohol followed by



Scheme 2 *Reagents and conditions*: i, LDA (2 equiv.), BOMCl, HMPA, −78 °C, 70%; ii, TBDMSCl, imidazole, DMF, 90%; iii, DIBAL-H, Et_2O, −78 °C, 86%; iv, $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, −65 to −55 °C; v, $(MeO)_2POCH_2CO_2Me$, LiCl, Pr^i_2NEt, MeCN, 84% for 2 steps; vi, DIBAL-H, Et_2O, −78 °C, 95%; vii, $Ti(OPr^i)_4$, D-(−)-diisopropyl tartrate, Bu^tOOH, 76.5%; viii, $Me_2Cu(CN)Li_2$, Et_2O, −20 to 0 °C, 72.4%; ix, TBDMSCl, Et_3N, DMAP, CH_2Cl_2, 84.4%; x, MsCl, pyridine, 97.7%; xi, NaN_3, DMF, 76.4%; xii, $Pd(OH)_2$, H_2 (1 atm,), MeOH, EtOAc; xiii, $ClCO_2Bn$, $NaHCO_3$, Et_2O, 0 °C, 51% for 2 steps; xiv, $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, −65 to 55 °C; xv, $NaClO_2$, 2-methylbut-2-ene, NaH_2PO_4, H_2O, Bu^tOH, 71% for 2 steps; xvi, Pd-black, MeOH, H_2 (1 atm); xvii, $(PyS)_2$, PPh_3, MeCN, reflux, 79% for 2 steps.

sequential azide substitution, reduction of the corresponding azide under Pd/C and the protection of the amino group with $ClCO_2Bn$ afforded **9** in 41% overall yield in four steps. Unfortunately attempts, including Mitsunobu conditions, to directly convert the alcohol to amine stereospecifically were not successful. This result may be due to the steric hindrance present in **8**. Swern oxidation of **9** led to the β-amino aldehyde, which was further oxidized to the corresponding acid **10** with $NaClO_2$. Finally removal of the Z group by catalytic hydrogenation followed by cyclization using Ohno's conditions[9] furnished the known key intermediate **11**.[10–12] The physicochemical properties of **11** obtained by the present synthesis were in complete agreement with those reported in the literature {$[\alpha]_D^{27}$ −7.8755 (*c* 0.53, $CHCl_3$) [lit,[12] $[\alpha]_D^{22}$−7.8777 (*c* 1.03, $CHCl_3$)]}.

In summary, we report a new synthetic method for the 1β-methylcarbapenem key intermediate from commercially available methyl (*R*)-3-hydroxybutyrate **4**. The key features in this strategy are the diastereoselective alkylation of the dianion of the β-hydroxy ester, Sharpless asymmetric epoxidation and subsequent regioselective cuprate ring opening of the chiral epoxide.

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Notes and references

1 D. H. Shih, F. Baker, L. Cama and B. G. Christensen, *Heterocycles*, 1984, **21**, 29.
2 K. Kondo, M. Seki, T. Kuroda, T. Yamanaka and T. Iwasaki, *J. Org. Chem.*, 1997, **62**, 2877.
3 For a review, see: A. H. Berks, *Tetrahedron*, 1996, **52**, 331 and references cited therein.
4 S. Hatakeyama, N. Ochi, H. Numata and S. Takano, *J. Chem. Soc., Chem. Commun.*, 1988, 1202.
5 R. E. Ireland and R. B. Wardle, *J. Org. Chem.*, 1987, **52**, 1780.
6 O. Muraoka, N. Toyooka, Y. Oshima, N. Narita and T. Momose, *Heterocycles*, 1989, **29**, 269.
7 Details will be published in full elsewhere.
8 M. A. Blanchette, W. Choy, J. T. Davis, A. P. Essenfeld, S. Masamune, W. R. Roush and T. Sakai, *Tetrahedron Lett.*, 1984, **25**, 2183.
9 S. Kobayashi, T. Iimori, T. Izawa and M. Ohno, *J. Am. Chem. Soc.*, 1981, **103**, 2406.
10 A. Sasaki, H. Masumura, T. Yano, S. Takata and M. Sunagawa, *Chem. Pharm. Bull.*, 1992, **40**, 1098.
11 Y. Ito, Y. Kimura and S. Terashima, *Bull. Chem. Soc. Jpn.*, 1987, **60**, 3337.
12 N. Tsukada, T. Shimada, Y. S. Gyoung, N. Asao and Y. Yamamoto, *J. Org. Chem.*, 1995, **60**, 143.

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