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A NEW ENANTIO AND DIASTEREOSELECTIVE SYNTHESIS OF 2-AZETIDINONES AS USEFUL INTERMEDIATES OF β-LACTAM ANTIBIOTICS

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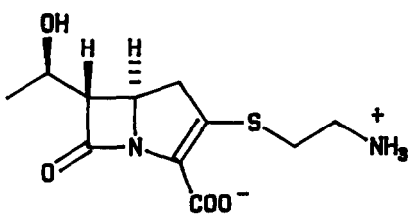
Summary: An expeditious enantio and diastereoselective route to β-lactam synthons has been developed; two novel key radical reactions allowed us to obtain two useful intermediates in the synthesis of thienamycin and PS-5.

Since 1976, after the isolation by a Merck research group[1] of (+)-thienamycin 1, a new carbapenem with important antibacterial activity, many efficient routes to 1 and penems 2 have been developed[2,3].

An important intermediate common to many routes is represented by 2-azetidinone 3, which has been obtained almost exclusively from natural - precursors[4]. In this communication we wish to describe a new enantio and diastereoselective synthesis of 2-azetidinones 16 and 19, starting from commercially available cis-2-buten-1,4-diol 4 (see scheme).



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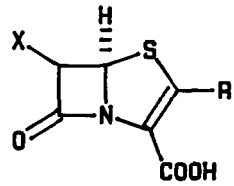

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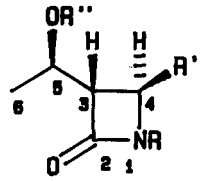

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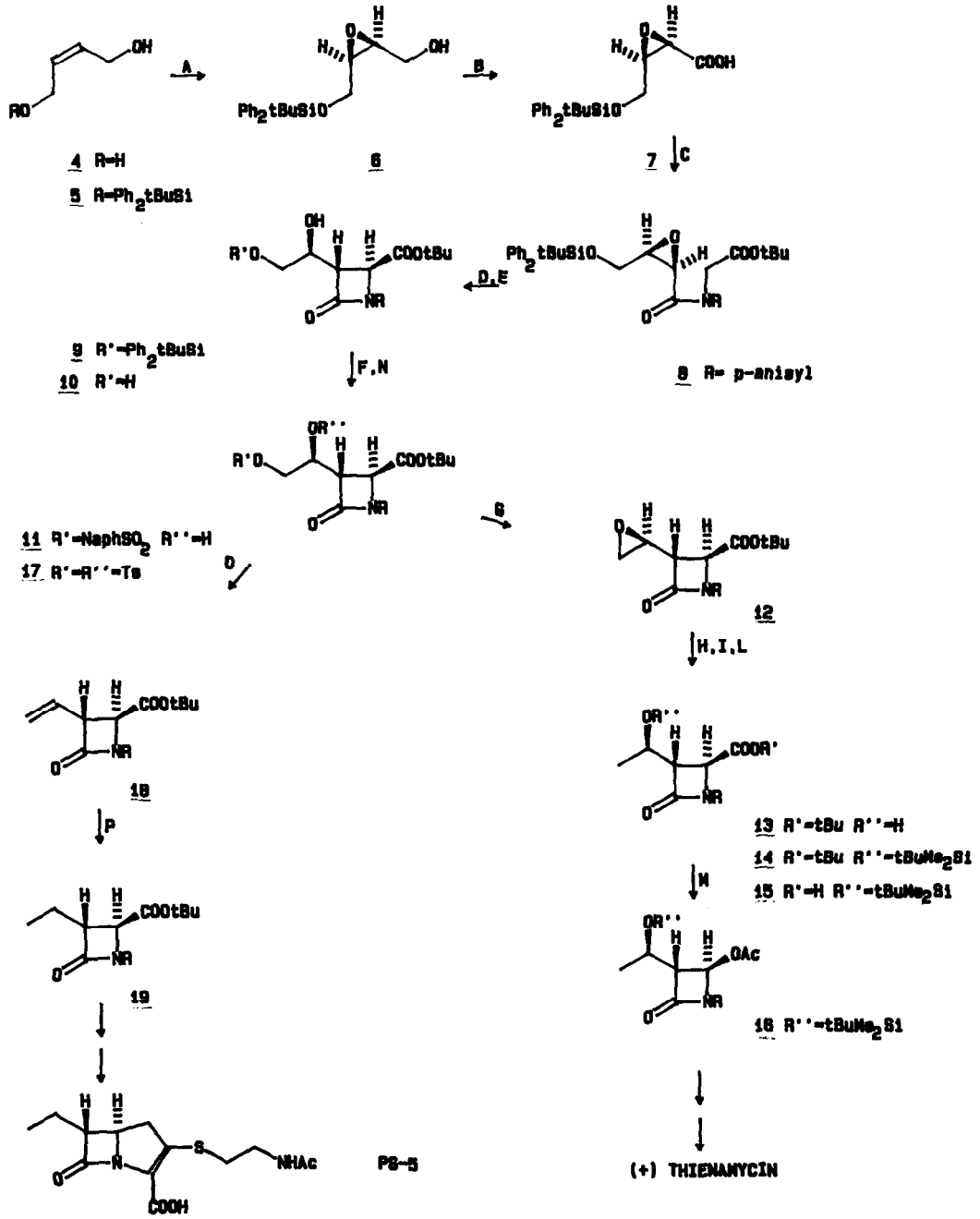
The monoprotected compound 5 ($tBuPh_2SiCl$, imidazole, DMF, r.t., 20 h, 30%) was epoxidized according to Sharpless[5], to afford the chiral epoxyalcohol 6[6] (90%). The subsequent oxidation of 6[7] to 7, was achieved in high yield buffering the reaction mixture with $NaHCO_3$. Compound 7[8] , which is formally related to the corresponding 2,3-epoxybutane acid prepared from L-threonine[3d], was transformed into the epoxyamide 8 (70% from 6). The latter was then subjected to the key cyclization step to afford β-lactam 9: the chosen conditions (LiHMDS, THF, T=-25·C) allowed us to obtain 9 as the only product (50% after purification by flash chromatography).



Reagents and conditions: A) $Ti(O\text{-}i\text{-}pr)_4$, L(+) DET, TBHP, CH_2Cl_2, T=-25·C (90%). B) $RuCl_3$, $NaIO_4$, $NaHCO_3$, H_2O, CH_3CN, CCl_4. C) p-MeO-C_6H_6-NH-$CH_2COOtBu$, ClCOOiBu, N-methylmorpholine, 4 sieves, THF, T=-25·C (70% from 6). D) LiHMDS, THF, T=-25·C, 15 min (50%). E) TBAF, THF, T=-20·C (90%). F) $NaphSO_2Cl$, Py, T= 0·C (85%). G) K_2CO_3, MeOH, T=-35·C, 10h (75%). H) NaI, n-Bu_3SnH, AIBN, DME, T=75·C, 2h,(80%). I) $tBuMe_2SiCl$, DMAP, imidazole, r.t., 20h (90%). L) NaOH (1.1 eq), EtOH, T=50·C, 8h. M) $Pb(OAc)_4$, DMF, AcOH, T=70·C, 45 min (60% from 14). N) TsCl, DMAP, CH_2Cl_2, rt, 12h (85%). O) NaI, n-Bu_3SnH, DME, AIBN, T=80 C, 24h (80%). P) Pd/C 10%, H_2 (1atm), MeOH (90%).

The correct relative stereochemistry of C-3 and C-4 was confirmed by ^{1}H-NMR decoupling. Careful deprotection of the primary hydroxyl function (T= -20·C), gave 10 in high yield (90%).

Because of the possibility of properly elaborating the hydroxy functions at C-5 and C-6, compound 10 appeared to be a new strategically important chiral synthon for the preparation of several different azetidinone intermediates.

Compound 12 was prepared from 10, via the mononaphthylsulphonyl derivative 11, achieving the epoxide formation at T=-35·C[9] and then succesfully transformed into 13 by a novel chemo and regioselective reductive opening of the epoxy ring (NaI, n-Bu_3SnH, DME, AIBN, T= 80·C, 2h, 80%)[10] in rather good yield (80%). In order to have a chemical correlation the hydroxyl function at C-5 was protected as t-$BuMe_2Si$ by standard procedure[11]. Alkaline hydrolysis of the ester function (NaOH 1.1 eq, EtOH), was followed by oxidative decarboxylation of the acid 15[12], affording known 16[13,14] (60% overall yield from 13).

On the other hand the key intermediate 10 was tosylated to 17 and, the latter, subjected to a novel radical elimination (NaI, n-Bu_3SnH, DME, AIBN, T= 80·C, 24h)[15]. The olefin 18, obtained as the only product of the reaction (80%) was finally hydrogenated to 19[16], a potential chiral intermediate for the synthesis of the β-lactam PS-5[17]. The smooth obtaining of terminal olefins from 1,2 ditosylated diols by radical elimination is now investigated on several other compounds.

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References and notes

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6) ^{1}H-NMR (60 MHz), $CDCl_3$: 7.6-7.0 ∂ (10H, aromatic portion), 3.6 ∂ (2H, m, CH_2-1), 3.4 ∂ (2H, m, CH_2-4), 3.0 ∂ (2H, m, CH-2, CH-3), 2.5 ∂ (1H, t, OH), 0.9 ∂ (9H, s, t-Bu). The optical purity of 6 has been determined by GLC and ^{19}F-NMR (ee>98%) on the corresponding MPTA ester (Mosher derivative).

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8) H^1-NMR (60MHz), $CDCl_3$: 9.3-8.8 ∂ (1H, bs,-COOH), 7.6-7.0 ∂ (10H, m, aromatic portion), 3.8 ∂ (2H, d, CH_2-4), 3.45 ∂ (1H, d, J=5Hz, CH-2), 3.3 ∂ (1H, m, CH-3), 1.0 ∂ (9H, s, t-Bu).

9) To avoid the formation of the eliminated product the temperature must be keep rigorously under -35·C, although with larger reaction time(10h).

10) For an extensive application of this reaction to various and different substrates see the following paper of this issue.

11) Alternatively the -OH at C-5 has been protected as THP, obtaining 13 (R"=THP) then transformed into 16 (R"=THP) by the described procedure. The THP group has been selectively removed in the same mild condition (AcOH, H_2O, THF, 3:3:1, T= 50·C, 1h, 90%).

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14) ^{1}H-NMR (300 MHz), $CDCl_3$: 7.37-6.86 ∂ (4H, dd, aromatic portion), 6.66 ∂ (1H, s, CH-4), 4.29 ∂ (1H, o, CH-5), 3.79 ∂ (3H, s, OCH_3), 3.20 ∂ (1H, dd, CH-3, J=3Hz), 2.13 ∂ (3H, s, $-OCOCH_3$), 1.35 ∂ (3H, d, J=6Hz, CH_3-6), 0.75 ∂ (9H, s, t-Bu), 0.1 ∂ (3H, s, $SiCH_3$), 0.08 ∂ (3H, s, $SiCH_3$).
$(\alpha)_D$ =-67.17· (c= 0.28, $CHCl_3$); lit: $(\alpha)_D$ =-66.86· (13). M.p.= 70-71.5·C. HRMS: requires m/e 393.1970, found m/e 393.1970.

15) For a related method of deoxygenation of primary hydroxyl group see: Y. Ueno, C. Tanaka and M. Okawara Chem. Lett., 795 (1983).

16)^{1}H-NMR (300 MHz), $CDCl_3$: 7.20-6.80 ∂ (4H, dd, aromatic portion), 4.05 ∂ (1H, d, J=2.5 Hz, CH-4), 3.79 ∂ (3H, s, $-OCH_3$), 3.22 ∂ (1H, m, CH-3), 2.0-1.73 ∂ (2H, m, CH_2-5), 1.45 ∂ (9H, s, t-Bu), 1.09 ∂ (3H, t, J=7.0Hz,CH_3-6).

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