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Preparation of Novel Tricyclic Diazo Carbapenems: Application of Inverse Electron Demand Diels-Alder Reactions of 3,6-Bis(methylthio)-1,2,4,5-tetrazine

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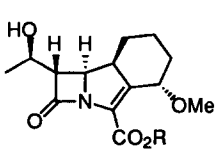
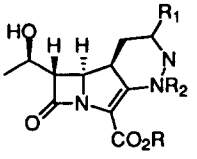
Abstract: The syntheses of novel tricyclic diazo carbapenem precursor **17**, and the deprotected carbapenems **2** and **3** are described. The construction of the tricyclic carbapenem was accomplished by an intramolecular nucleophilic substitution of the diazine sulfone **16** which was obtained from an inverse electron demand Diels-Alder reaction of the alkynyl azetidinone **13** with 3,6-bis(methylthio)-1,2,4,5-tetrazine (**4**).

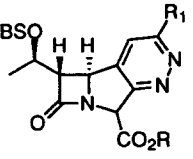
Recent reports of the tricyclic carbapenem GG-326 (formerly referred to as GV 104326) and its orally active pro-drug ester have generated considerable attention due to their broad spectrum of antibacterial activity and resistance to hydrolysis by the beta-lactamases as well as the renal dehydropeptidases.[1] Many heterocyclic variants of the tricyclic carbapenems have been detailed in the literature,[2] but none have been reported with a nitrogen atom directly attached to the 2-position (Figure 1). We wish to report the synthesis of a novel tricyclic diazo carbapenem intermediate **17**, a potential precursor to the diazo carbapenem analogues of GG-326, and its' deprotection products **2** and **3** with a nitrogen atom directly attached to the 2-position of the carbapenem ring system.



1 R = H (GG-326)



Tricyclic Diazo Carbapenem



17 R = Bn, R_1 = SO_2Me
2 R = Na, R_1 = SO_2Me
3 R = Na, R_1 = H

Figure 1. Tricyclic carbapenems

The retrosynthetic analysis of the tricyclic diazo carbapenem is shown in Figure 2. The final ring closure to the carbapenem skeleton is envisioned to take place via intramolecular nucleophilic displacement of the pyridazinyl sulfone. Although it would be desirable to have the orientation of the carboxylate in the alpha

position as in the penicillin structure, the stereochemistry is not critical since it will be converted to the olefin at a later stage. Previous reports of intramolecular cyclizations to form carbapenem skeletons have been shown to produce a single diastereomeric product.[3] The cyclization precursor can be formed by inverse electron demand Diels-Alder reaction of the electron-deficient 3,6-bis(methylthio)-1,2,4,5-tetrazine (**4**)[4] with an appropriate azetidinone alkyne or olefin. Among many of the electron-deficient azadiene systems, the electron-deficient symmetrically disubstituted tetrazines **4** and **5** have been studied widely and have been an effective source for the preparation of heterocyclic systems not easily attainable by other methods.[5,6,7]

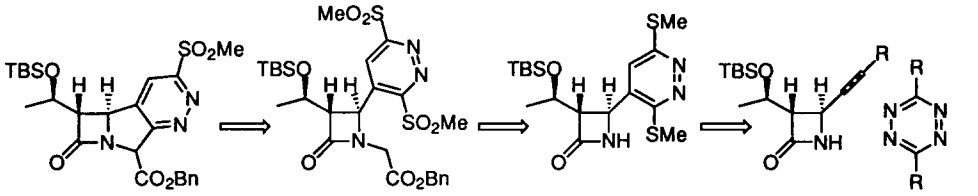
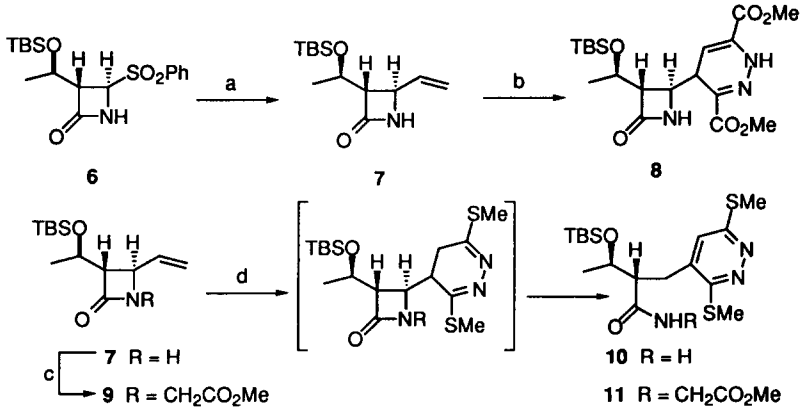


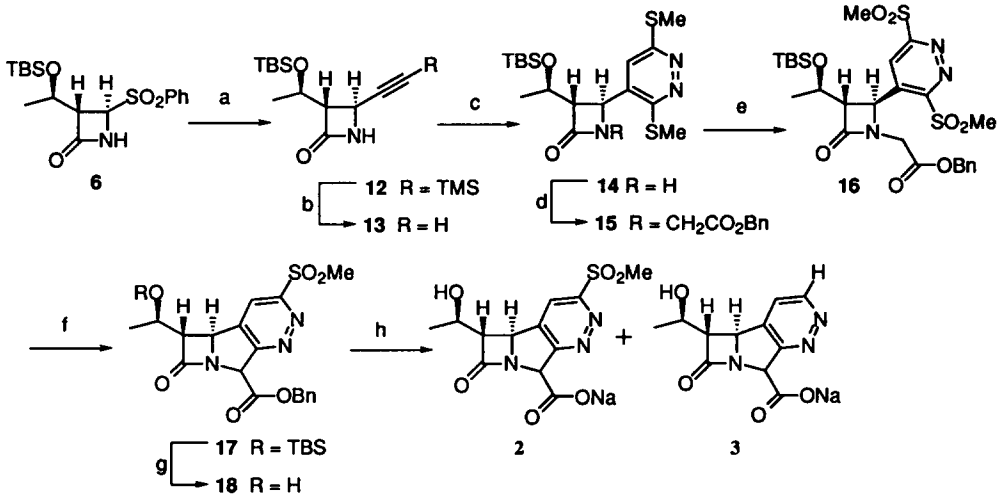
Figure 2. Retrosynthetic analysis



Scheme 1. (a) vinylmagnesium bromide, THF, -78°C-0°C, 4 h, 90%; (b) **5**, CH_2Cl_2, rt, 4 d, 57%; (c) LHMDS, methyl bromoacetate, THF, -78 °C - 0 °C, 78%; (d) For**10** **4**, dioxane, 80 °C, 48 h, 101 °C, 24 h, 49%; For **11**: **4**, p-xylene, 140 °C, overnight, 57%.

Since olefins are more reactive towards azadienes in the inverse Diels-Alder reactions, the vinyl azetidinone was first utilized as the dienophile partner. Reaction of the vinyl magnesium bromide with the phenyl sulfonyl azetidinone **6** provided the vinyl azetidinone 7 in 90 % yield. Initial Diels-Alder reaction with

the more reactive tetrazine **5**[8] proceeded at room temperature to give the desired dihydro pyridazinyl azetidinone **8** in 73% yield. However the reaction of either azetidinones **7** or **9**, obtained from **6** (LHMDS, methyl bromoacetate, 78%), with the bis-methylthio tetrazine **4** was sluggish and had to be heated to 110 °C to 140 °C for completion of the reaction. Under these thermal reaction conditions, the rearranged products **10** and **11** were isolated.



Scheme 2. (a) TMS acetylene, MeMgBr, THF,rt, 3h; **6**, THF, -78 °C - rt, 4 h, 70%; (b) $AgNO_3$, KCN, MeOH, H_2O, RT, 100%; (c) **4**, xylene, 140 °C, 3 d, 37%; (d) LHMDS, benzyl bromoacetate, -78 °C - rt, 2 h, 95%; (e) *m*CPBA, CH_2Cl_2, 0 - rt, overnight, 80%; (f) LHMDS, -60 °C, 3 h, 67%; (g) TBAF, HOAc, THF, 0 °C - rt, 24h, 73%; (h) 10% Pd-C, $NaHCO_3$, H_2, EtOAc:H_2O (3:2), 10 h, 36%(**2**), 48%(**3**).

The alkynyl azetidinone, which would provide the pyridazine ring directly after the Diels-Alder reaction and thus could potentially avoid the rearrangement from taking place, was used next as dienophile. Thus treatment of **6** with the TMS protected alkynyl magnesium bromide resulted in clean conversion to **12** in 70% yield which was deprotected in quantitative yield to give **13**.[9] Subjection of the alkynyl azetidinone **13** to the Diels-Alder conditions (xylene, 140 °C) gave the desired cycloadduct **14** in 37% yield with some recovered azetidinone as well as the tetrazine. Prolonged reaction times (>3 days) resulted in disappearance of the tetrazine without improvement in the yields. Elaboration to the sulfone **16** was accomplished by reaction with benzyl bromoacetate followed by oxidation with *m*CPBA. Treating the sulfone **16** with two equivalents of lithium hexamethyl disilazane at -78 °C resulted in ring closure to the desired carbapenem skeleton in 67% yield as a single diastereomer. Use of one equivalent of the base did not result in ring closure. Removal of the

TBS group (TBAF, AcOH) followed by hydrogenolysis of the benzyl group (H_2, Pd/C, $NaHCO_3$) gave unexpectedly two products, **2** and **3**. Under the hydrogenolysis conditions, the sulfone group had been replaced by a hydrogen. Both compounds turned out to be inactive in *in vitro* antibacterial assays. A similar aryl tricyclic carbapenem with 6β-amido substituent and an alpha-carboxylate stereochemistry has been reported to have only marginal activity.[10]

We were unable to crystallize either **17** or **18** for stereochemical determination. ^{1}H NMR NOE's were not useful in determining the stereochemistry. However, the coupling constant of 1.2 Hz observed between the C5-H and C3-H indicates the orientation of the carboxylate to be in the beta position. No isomerization of the stereochemistry was observed during the deprotection of the TBS group.[11]

In summary, the construction of the tricyclic diazo carbapenem intermediate, which can potentially be converted to the desired delta-2 carbapenem, have been demonstrated via a novel intramolecular nucleophilic substitution reaction.

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