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Silver Mediated Cyclizations of 4-Allenyl–and 4-(2-Propynyl)azetidinones. A Stereoselective Synthesis of 3-Substituted Δ^1-Carbapenems Via N–C3 Closure.

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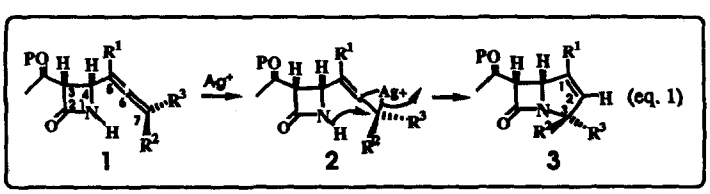
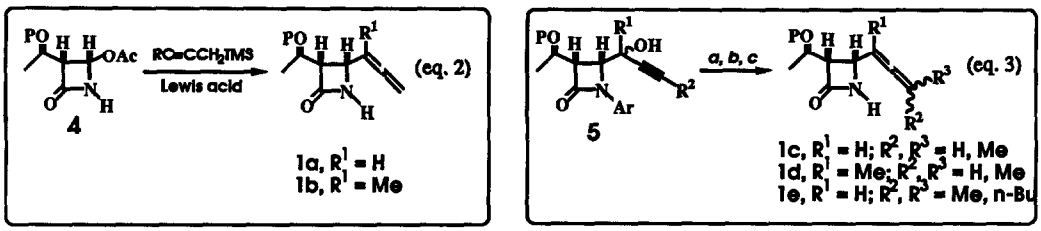
Abstract: A silver catalyzed cyclization of 4-allenylazetidinones to Δ^1–carbapenems and of 4-(2-propynyl)-azetidinones to Δ^2–carbapenems is described. The silver mediated cyclization is stereospecific: starting with stereodefined 4-allenylazetidinones, specific stereoisomers of C–3 substituted Δ^2–carbapenems can be prepared.

As part of our recent study of the stereoselective synthesis of 1-β-methylcarbapenem precursors utilizing a highly stereoselective reduction of a $Co_2(CO)_6$ stabilized propargylic cation, we had occasion to prepare a variety of 4-(3-propynyl)– and some 4-allenyl–substituted azetidinones.[2] These unsaturated substrates appeared ideally suited for conversion into Δ^2-carbapenems and Δ^1-carbapenems, respectively, via N–C3 bond formation on treatment with appropriate electrophiles.[3] In the present paper we describe our efforts utilizing a silver mediated process to effect N–C3 bond formation.

Silver and mercury mediated heterocycle formation via cyclization of allenes bearing internal oxygen and nitrogen nucleophiles has been described recently.[4] Application of this chemistry to 4-allenyl azetidinones **1** would provide a simple route to Δ^1-carbapenems **3** and probably proceed in a stereospecific fashion via the Ag-bridged cation **2** (eq. 1). Five representative allenes were studied in this chemistry. The simple allenes **1**, $R^1 = R^2 = R^3 = H$ and $R^1 = Me$, $R^2 = R^3 = H$ were prepared from the 4-acetoxyazetidinone **4**[5] by Lewis acid induced reaction with $Me_3SiCH_2C{\equiv}CH$ and $Me_3SiCH_2C{\equiv}CCH_3$, respectively (eq. 2: 1a – 4.5 equiv 3-trimethylsilyl-1-propyne, $BF_3{\cdot}Et_2O$, hexane, rt, 71%; 1b – 3 equiv. 1-trimethylsilyl-2-butyne, 1.9 equiv trimethylsilyltriflate, CH_2Cl_2, -5°C, 65%).[6] For substrates **1** with R^2 or $R^3 \neq H$, diastereomeric mixtures of allenes were prepared by the S_N2' reaction of MeMgBr / CuBr / LiBr with the mesylates prepared from the propargyl alcohol epimeric mixtures **5**, Ar = 4-$MeOC_6H_4$ (eq. 3: 1c – 77%, 2.0:1 mixture of diastereomers; 1d – 36%, 2.5:1 mixture of diastereomers; 1e – 52%, 2.2:1 mixture of diastereomers). The requisite propargyl alcohols were made by nucleophilic addition to 4-acylazetidinones[7] which are readily available via the chemistry described in our earlier paper.[2]





P = t-butyldimethylsilyl; Ar = p-methoxyphenyl

a, base / CH_3SO_2Cl; *b*, MeMgBr / CuBr / LiBr; *c*, CAN

All allenes reacted smoothly with $AgBF_4$ in CH_2Cl_2 at room temperature and formed Δ^1-carbapenems **3** in good yields (Table). Allenes **1a** and **1b** could be cyclized to carbapenems **3a** and **3b** with as little as 0.1eq. of $AgBF_4$, although reaction times could be reduced considerably by using 0.5 equivalents of the reagent. Ring closure reactions of the allenes **1c-e** having substituents at the terminal sp^2 carbon atom involved in the N-C bond formation were noticeably slower and required a minimum of 0.5 to 1 equivalent of the Ag reagent for efficient formation of the products **3c-e**, each as a mixture of diastereoisomers. Interestingly, cyclization of allene **1e** with less than 1 equiv of $AgBF_4$ provided the expected mixture of Δ^1-carbapenem diastereomers **3e**, while only one diastereomer (structure **11** in text below) was formed in 43% yield when 1 equiv of $AgBF_4$ was used. An equilibration mechanism (vida infra) is presumably responsible for this phenomenon.

Table. Silver Induced Cyclization of 4-Allenylazetidinones to Δ^1-Carbapenems (1→3).

entry	allene	$AgBF_4$ equiv	time (hr)	product	yield (%)	diast.
1	**1a**	0.50	2	**3a**, R^1=R^2=R^3=H	75	—
2	**1b**	0.14	8	**3b**, R^1=Me; R^2=R^3=H	70	—
3	**1c**	1.0	15	**3c**, R^1=H; R^2, R^3=H, Me	65	1:2.0
4	**1d**	1.3	15	**3d**, R^1=Me; R^2, R^3=H, Me	62	1:2.8
5	**1e**	0.5	18	**3e**, R^1=H; R^2, R^3=Me, n-Bu	58	1:2.2

Consideration of the stereoelectronic requirements inherent in the Ag+ induced transformation shown in equation 1 suggested that the use of single diastereomers of the allenes **1c-e** could result in ring closure to a stereodefined carbapenem. To address this issue, allene **1e** was prepared in a stereospecific fashion. Reduction of alkynone **6**[8] with L-Selectride gave propargyl alcohol **7**, exclusively, in high yield (90%).[9] The epimeric alcohol **8** was readily prepared by Mitsunobo[10] inversion of **7** via the intermediate benzoate ester. Treatment of the epimeric mesylates of **7** and **8** with MeMgBr / CuBr / LiBr proceeded with complete stereoselectivity to provide, after N-deprotection with ceric ammonium nitrate, allenes **9** and **10**, respectively. Assignment of stereochemistry to the diastereomeric allenes was based on literature precedent[11] documenting the anti-S_N2' pathway for organocopper additions to propargylic systems. Treatment of **9** with 1 equivalent of $AgBF_4$ in CH_2Cl_2 for 18 hr gave only carbapenem **11** in 60% yield which is consistent with anti opening of the Ag-bridged cation **2**. Interestingly, the diastereomeric allene **10** also gave **11** under identical conditions; however, the anticipated carbapenem **12** was formed exclusively (60%) when only 0.5 equivalents of $AgBF_4$ were used. We have not yet probed this interesting aspect of the silver induced ring closure, but it is possible that diastereomer **11**, the sterically less hindered product, might be formed by equilibration of **12** in the presence of excess $AgBF_4$ via silver induced ionization of the allylic amide moiety to an allylic cation.

Support for the assignment of stereochemistry to the product carbapenems **11** and **12** was achieved by analysis of ^{1}H NMR chemical shifts and NOE difference spectra. Molecular models indicated that the β–methyl group at C–3 of **11** would experience anisotropic deshielding by the β–lactam carbonyl group. The methylene group of the β–butyl group of **12** should experience a similar deshielding. In accord with this analysis the following data are observed: **11**: CH_3, δ1.50; CH_2, δ1.27; **12**: CH_3, δ1.12; CH_2, δ2.05-1.84. A weak but reproducible NOE enhancement was observed for the H–5 methine signal by irradiating at either the α–n-butyl methylene group of **11** or the α–methyl group of **12** confirming the syn nature of these groups.

Attempts to apply this same methodology to the silver mediated cyclization of 4-(2-propynyl)azetidinones were only moderately successful. A variety of alkynyl substituted azetidinones were prepared, but only compounds **14**[13] and **15**[14], prepared from terminal alkyne **13**,[12] could be successfully cyclized. In these cases only $AgNO_3$ gave the desired product (eq. 4).

In conclusion, silver mediated N–C3 bond formation by electrophile induced ring closure of 4-(allenyl) and 4-(2-propynyl)azetidinones provides a rapid method for construction of numerous Δ^1–carbapenems and some Δ^2–carbapenems. The ring closure on the 4-allenylazetidinones occurs in a stereospecific fashion providing a means of controlling the stereochemistry of substituents at C–3 of the Δ^1–carbapenem.

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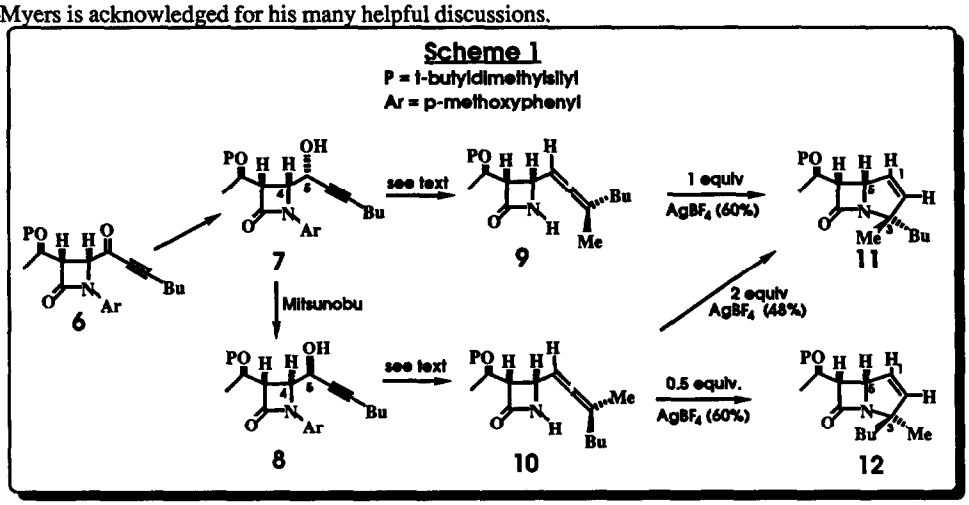
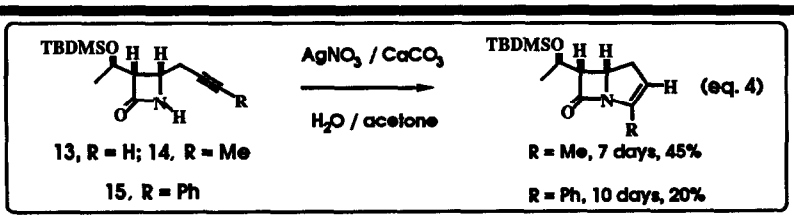
Scheme 1

P = t-butyldimethylsilyl
Ar = p-methoxyphenyl





References and Notes

1 Fellow of the Alfred P. Sloan Foundation, 1983–1987; Camille and Henry Dreyfus Foundation Teacher–Scholar, 1986–1991.

2 Prasad, J. S.; Liebeskind, L. S. Tetrahedron Lett., **1987**, *28*, 1857–1860.

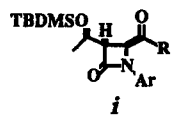
3 A multistep Hg(+2) based method for N–C3 bond formation recently has been described: Dumas, F.; d'Angelo, J. Tetrahedron Lett., **1986**, *27*, 3725–3728. For a brief discussion of N-C3 bond formation in penems and carbapenems see Wasserman, H. H.; Han, W. T. J. Am. Chem. Soc., **1985**, *107*, 1444.

4 (a) Claesson, A.; Sahlberg, C.; Luthman, K. Acta Chem. Scand. B, **1979**, *33*, 309–310. (b) Olsson, L-I.; Claesson, A. Synthesis, **1979**, 743–745. (c) Audin, P.; Doutheau, A.; Ruest, L.; Goré, J. Bull. Soc. Chim. Fr., **1981**, 313–318. (d) Audin, P.; Doutheau, A.; Goré, J. Tetrahedron Lett., **1982**, *23*, 4337–4340. (e) Arseniyadis, S.; Goré, J. Tetrahedron Lett., **1983**, *37*, 3997–4000. (f) Arseniyadis, S.; Sartoretti, J. Tetrahedron Lett., **1985**, *26*, 729–732. (g) Lathbury, D.; Gallagher, T. J. Chem. Soc., Chem. Commun., **1986**, 1017–1018. (h) Delair, T.; Doutheau, A. Tetrahedron Lett., **1986**, *27*, 2859–2860. (i) Chilot, J. J.; Doutheau, A.; Goré, J.; Saroli, A. Tetrahedron Lett., **1986**, *27*, 849–852. (j) Grimaldi, J.; Cormons, A. Tetrahedron Lett., **1986**, *42*, 5089–5090. (k) Walkup, R. D.; Park, G. Tetrahedron Lett., **1987**, *28*, 1023–1026. (l) Pale, P.; Chuche, J. Tetrahedron Lett., **1987**, *28*, 6447–6448.

5 (a) Fuentes, L. M.; Shinkai, I.; Salzmann, T. N. J. Am. Chem. Soc., **1986**, *108*, 4675. (b) Nagoa, Y.; Kumagai, T.; Tamai, S.; Abe, T.; Kuramoto, Y.; Taga, Y.; Aoyagi, S.; Nagase, Y.; Ochiai, M.; Inoue, Y.; Fujita, E. J. Am. Chem. Soc., **1986**, *108*, 4673. (c) Dáziel, R.; Favreau, D. Tetrahedron Lett., **1986**, *27*, 5687. (d) Shibata, T.; Iino, K.; Tanaka, T.; Hashimoto, T. Tetrahedron Lett., **1985**, *26*, 4739. (e) Chiba, T.; Nagatsuma, M.; Nakai, T. Chemistry Lett., **1985**, 1343. We thank Bristol–Myers, France for a generous supply of compound **4**.

6 All new compounds were fully characterized by IR and high field ^{1}H NMR spectroscopy and by high resolution mass spectroscopy. ^{13}C NMR was also used when neccessary.

7 Compound **5**, $R^1 = R^2 = H$ was prepared from *i*, R = C≡CSiMe$_3$,[2] by reduction with $NaBH_4$ (100%) followed by desilylation with $AgNO_3$ / KCN (90%). Compound **5**, R^1 = Me, R^2 = H was prepared from *i*, R = CH_3,[2] by addition of LiC≡CSiMe$_3$ (73%) followed by desilylation with $AgNO_3$ / KCN (90%). Compound **5**, R^1 = H, R^2 = n-Bu was prepared from *i*, R = C≡CBu, synthesized according to the method described in reference 2, by reduction with $NaBH_4$ (100%).



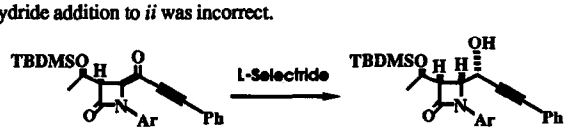
i

8 Prepared according to the procedure described in reference 2.

9 Assignment of stereochemistry was based on ^{1}H NMR vicinal coupling constants, $^3J_{4,5}$. Literature data (below) and our own results for a variety of 4-substituted azetidinones similar to **7** and **8** indicates that $^3J_{4,5}$ for the 4RS, 5SR relative stereochemistry is smaller than $^3J_{4,5}$ for the 4RS, 5RS relative stereochemistry. For **7** (4S, 5R), $^3J_{4,5}$ = 2.0 Hz while for **8** (4S, 5S), $^3J_{4,5}$ = 4.9 Hz.

(a) Takahashi, Y.; Yamashita, H.; Kobayashi, S.; Ohno, M. Chem. Pharm. Bull. Jpn., **1986**, *34*, 2732–2742. (b) Bateson, J. B.; Quinn, A. M.; Southgate, R. Tetrahedron Lett., **1987**, *28*, 1561–1564. A discussion relevant to the possible transition states of the nucleophilic additions to **6** is contained in: Takahashi, T.; Miyazawa, M.; Tsuji, J. Tetrahedron Lett., **1985**, *26*, 5139–5142.

This detailed ^{1}H NMR analysis allows us to correct our original assigment of 5S stereochemistry to the L-Selectride reduction product of azetidinone *ii* in our earlier paper.[2] For the reduction product *iii*, $^3J_{4,5}$ = 2.2 Hz dictating 5R stereochemistry. This correction does not affect the main substance of our results described in reference 2, but does imply that our transition state rationalization for the hydride addition to *ii* was incorrect.



ii *iii*

10 Mitsunobu, O. Synthesis, **1981**, 1.

11 Marek, J.; Mageney, P.; Alexakis, A.; Normant, J. F. Tetrahedron Lett., **1986**, *27*, 5499–5502 and references therein.

12 Preparation: Treatment of 4-acetoxyazetidinone **4** with 2.1 equiv allenyltri-n-butylstannane and 1.9 equiv of $Me_3SiOSO_2CF_3$ in CH_2Cl_2 at rt gave **13** in 85% yield. Compound **13** was previously prepared by the addition of propargylmagnesium bromide to 4-(phenylsulfonyl)azetidinone: Shibasaki, M.; Nishida, A.; Ikegami, S. J. Chem. Soc., Chem. Commun., **1982**, 1324.

13 Preparation: Compound **13** was treated with t-butyldimethylsilyl chloride, Et_3N, DMF at rt to give the N-protected azetidinone in 89% yield. Methylation of the terminal alkyne was accomplished by deprotonation with $LiN(SiMe_3)_2$ in THF at -40°C followed by addition of $CH_3OSO_2CF_3$ (90% yield) and then selective desilylation of the protected nitrogen atom ($n\text{-}Bu_4N^+F^-$, THF, rt) gave compound **14** in 60% yield.

14 Preparation: Compound **13** was phenylated to give **15** in 94% yield according to the procedure in Dieck, H. A.; Heck, R. F. J. Organometal. Chem., **1975**, *93*, 259 (0.022 equiv. $PdCl_2(PPh_3)_2$, 0.022 equiv. CuI, 0.96 equiv. iodobenzene in 16 equivalents of Et_3N at rt).

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