Tetrahedron Letters,Vol.28,No.17,pp 1857-1860,1987 0040-4039/87 $3.00 + .00
Printed in Great Britain Pergamon Journals Ltd.

ACYCLIC STEREOCHEMICAL CONTROL USING HEXACARBONYLDICOBALT STABILIZED PROPARGYL CATIONS. A HIGHLY STEREOSELECTIVE ROUTE TO 1β-METHYLCARBAPENEM PRECURSORS.

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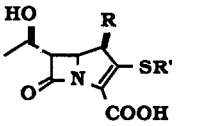
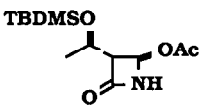
Abstract: A highly stereoselective route to precursors of 1β-methylcarbapenems is described. Hydride reduction of a hexacarbonyldicobalt stabilized propargyl cation derived from a 4-acyl-2-azetidinone prepared using the Weinreb ketone synthesis proceeds with complete stereochemical control to a 1β-methylcarbapenem precursor bearing an alkynyl unit. The alkyne is readily elaborated to (3S,4R)-3-[(1R)-1-t-butyldimethylsilyloxyethyl]-4-[(1R)-1-methyl-3-methoxycarbonyl-2-oxopropyl]-2-azetidin-2-one or hydrogenated and oxidatively cleaved to (3S,4S)-3-[(1R)-1-t-butyldimethylsilyloxyethyl]-4-[(1R)-1-carboxyethyl]-azetidin-2-one.

Carbapenems such as thienamycin 1 have attracted much attention in recent years because of their broad spectrum antibacterial properties.[2] The wide spread utility of these potent antibiotics has been hindered by both their chemical instability and their metabolic sensitivity to renal dehydropeptidase-I, but recent disclosures by Merck have demonstrated that the introduction of a β-methyl substituent at the C-1 position of the carbapenem nucleus provides an equally potent antibiotic 2 with substantially increased chemical and metabolic stability.[3] To date, the stereoselective introduction of the 1β-methyl substituent has been accomplished via total synthesis using an aldol-like condensation on the available azetidinone acetate 3[4], by hydride reduction of an olefinic precursor,[5] by stereoselective methylation of an enolate,[6] or from intermediates already containing the desired methyl group.[7] We wish to report a completely novel approach to 1β-methylcarbapenem precursors through the use of a highly stereoselective reduction of a hexacarbonyldicobalt stabilized propargyl cation prepared from the starting material 4.[8]



1 R = H, R' = $CH_2CH_2NH_2$
2 R = Me, R' = $CH_2(NMe_2)=NH_2$



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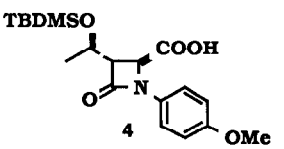
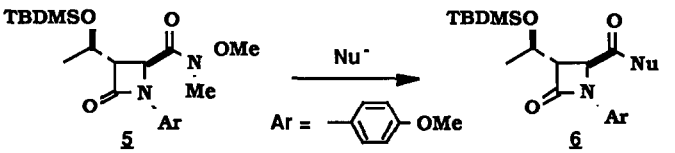


4

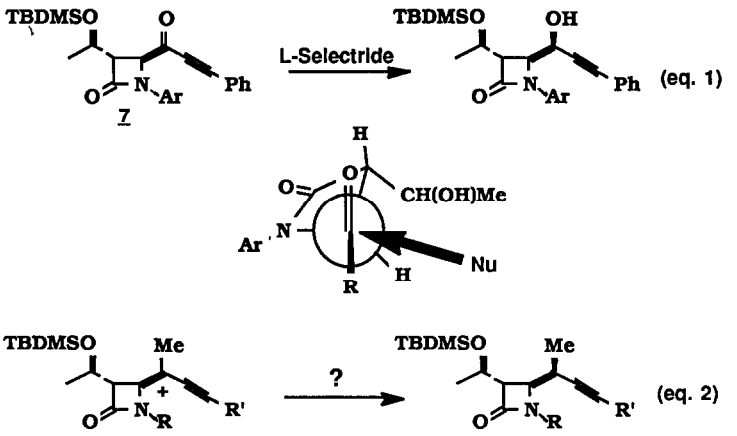
We have discovered that the carboxylic acid group of **4**, through the use of the N-methylhydroxamic acid O-methyl ether derivative **5** (Weinreb ketone synthesis),[9] provides a useful handle for elaborating **4** into a variety of functionalized 4-acylated monocyclic β-lactams **6** (Table 1). During an investigation of the reaction chemistry of some of the β-lactam ketones, a highly stereoselective reduction of **7** with L-Selectride at -78°C was observed to give only one alcohol in 90% yield (eq. 1). Felkin-Ahn[10] rationalization of nucleophilic attack on the chiral ketone suggested that the observed stereoisomer might be formed by hydride attack from the α-face providing the β-OH isomer of the product. While use of the Felkin-Ahn rule with a methyl substituted carbocation as a carbonyl equivalent might be an overextension of the model, we considered the hypothetical reduction shown in eq. 2 as a means for preparing a product bearing the desired β-methyl stereochemistry . A hexacarbonyldicobalt stabilized propargyl cation derived from **8** in Table 1 allowed this hypothesis to be probed (Scheme 1).

Table 1. Synthesis of β-Lactam Ketones and an Aldehyde via the Weinreb Ketone Synthesis.[1]



Entry	Nu^-	Nu^- equiv	T °C	Product, 6, Nu =[2]	Yield[3]
1	$LiAlH_4$	1.1	-70°	H[4]	80%
2	MeMgBr	2.0	0°	Me (**8**)	99%
3	PhC≡CLi	2.0	-10°	C≡CPh (**7**)	93%
4	TMSC≡CLi	2.0	-20°	C≡CTMS	75%
5	$MeOCH_2C{\equiv}CLi$	2.0	5°	$C{\equiv}CCH_2OMe$	78%
6	$CH_2{=}CHMgBr$	2.5	50°	$CH{=}CH_2$	45%
7	$CH_2{=}CHCH_2MgBr$[5]	2.0	0°	$CH_2CH{=}CH_2$	99%
8	$CH_2{=}CHCH_2MgBr$[6]	2.0	0°	*E*-$CH{=}CHCH_3$	99%
9	PhSCH(OMe)Li	1.0	-10°	CH(OMe)SPh	83%
10	$PhCH_2MgCl$	2.0	50°	CH_2Ph	47%
11		1.0	0°		62%
12		2.0	-50°		52%

[1] A THF solution of **5** was added to the nucleophile in THF under Ar at the indicated reaction temperature.
[2] All new compounds gave satisfactory spectral and analytical data.
[3] Yield refers to pure products isolated by flash column chromatography on SiO_2 unless otherwise noted.
[4] This unstable aldehyde has been mentioned in Hart, D. J., Ha, D.-C. *Tetrahedron Lett.*, 1985, 5493.
[5] The β,γ-unsaturated reaction product was obtained by quenching the reaction mixture with NH_4Cl, extracting with EtOAc, and then rapidly chromatographing the crude product on neutral alumina.
[6] The α,β-unsaturated reaction product was obtained by taking the crude reaction product from entry 7 and exposing it to basic Al_2O_3 until ^1H NMR monitoring showed the isomerization to be complete.



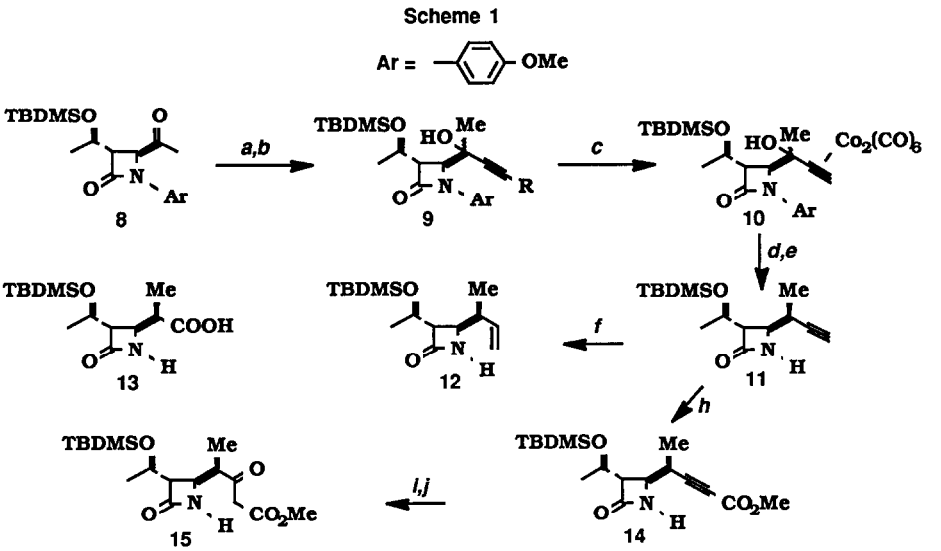
Treatment of acetylenic ketone 8 with TMSC≡CLi at 0°C in THF gave a 50:50 mixture of epimeric alcohols 9 (R = TMS) in 73% yield. Desilylation to 9 (R = H) was accomplished in 90% yield with $AgNO_3$ / KCN.[11] Complexation of the alkyne functionality to a $Co_2(CO)_6$ unit to give 10 was effected by reaction with 1.5 eq. $Co_2(CO)_8$ at rt in pet ether (68%). Reduction of the complexed propargyl alcohol (OH→H, 69%) was achieved using the Maryanoff modification (BH_3•SMe_2/TFA)[12] of the Nicholas reaction.[13] After simultaneous deprotection of the β-lactam nitrogen and decomplexation of the alkyne from the $Co_2(CO)_6$ fragment using ceric ammonium nitrate, high field ^1H NMR analysis of the alkyne product 11 (50%) showed the presence of only one of the two possible isomeric products. Confirmation of the β-methyl stereochemistry was arrived at by Lindlar reduction (100%) of 11 to the the previously known alkene 12[14] which was oxidatively cleaved (70%) to the carboxylic acid 13, a molecule of demonstrated utility in the synthesis of 1β-methylcarbapenems.[3a,c,4,5]

The acetylenic β-lactam 11 was also transformed into a ketoester, a functionality of potential value in the synthesis of 1β-methylcarbapenems. The alkyne 11 was readily carbomethoxylated (10% $PdCl_2$, 2 eq. $CuCl_2$, 1 atm CO, 2 eq. NaOAc, MeOH) to the acetylenic ester 14 in 66% yield.[15] Following a procedure used in the thienamycin series,[16] ester 14 was treated with thiophenoxide, then N-bromoacetamide followed by a reductive workup to provide the ketoester 15 in 60% yield with complete retention of the β-methyl stereochemistry. The ketoester existed as a mixture of keto and enol tautomers (3 : 1 ratio verified by IR, ^1H NMR and ^{13}C NMR).

We have shown that hexacarbonyldicobalt stabilized propargyl cations have unique potential in the control of stereochemistry in complex natural products.[17] Together with the Weinreb ketone synthesis, the Nicholas reaction has provided us with a unique and simple entry to precursors of 1β-methylcarbapenems.

Acknowledgements: We thank Bristol-Myers Company for support of this research. We are particularily indebted to Dr. Robert Morin of Bristol-Myers for many helpful discussions.

Scheme 1



(a) LiC≡CTMS, THF, 0°C, 73%; (b) $AgNO_3$, KCN, 90%; (c) $Co_2(CO)_8$, pet. ether, rt, 68%; (d) TFA / BH_3•Me_2S, 69%; (e) $(NH_4)_2Ce(NO_3)_6$, 50%; (f) H_2, Pd / $BaSO_4$, quinoline, 100%; (g) $RuCl_3$, $NaIO_4$, 70%; (h) $PdCl_2$, $CuCl_2$, NaOAc, CO, MeOH, 66%; (i) PhSH, Et_3N, THF, 100%; (j) NBA, dioxane-H_2O then Na_2SO_3, 60%

References and Notes

1. Fellow of the Alfred P. Sloan Foundation, 1983 - 1987; Camille and Henry Dreyfus Teacher Scholar, 1986 - 1991.
2. a. Ratcliffe, R. W.; Albers-Schonberg, G. "The Chemistry of Thienamycin and Other Carbapenem Antibiotics", in "Chemistry and Biology of β-Lactam Antibiotics", Vol. 2, Morin, R. B.; Gorman, M, Eds.; Academic Press: New York, 1982, p. 227. b. Kametani, T.; Fukumoto, K.; Ihara, M. Heterocycles, 1982, 17, 463.
3. a. Shih, D. H.; Baker, F.; Cama, L.; Christensen, B. G. *Heterocycles*, 1984, *21*, 29. b. Shih, D. H.; Fayter, J. A.; Cama, L. D.; Christensen, B. G.; Hirshfield, J. *Tetrahedron Lett.*, 1985, *26*, 583. c. Shih, D. H.; Cama, L.; Christensen, B. G. *Tetrahedron Lett.*; 1985, *26*, 587.
4. 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. Daziel, 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.
5. Iimori, T.; Shibasaki, M. *Tetrahedron Lett.*, 1986, *27*, 2149.
6. See reference 3a.
7. a. Reference 3b. b. Brown, P.; Southgate, R. *Tetrahedron Lett.*, 1986, *27*, 247.
8. We thank Bristol-Myers, France for a generous supply of (4S)-t-butoxycarbonyl-(3S)-[(1R)-hydroxyethyl-1-(4-methoxyphenyl) azetidinone which was converted into 4 by standard procedures.
9. Nahm, S.; Weinreb, S. M. *Tetrahedron Lett.*, 1981, *22*, 3815.
10. a. Cherest, M.; Felkin, H.; Prudent, N. *Tetrahedron Lett.*, 1968, *18*, 2199. b. Anh, N. T.; *Top. Curr. Chem.*, 1980, *88*, 145.
11. Schmidt, H. M.; Arens, J. F. *Recueil*, 1967, *86*, 1138.
12. McComsey, D. F.; Reitz, A.B.; Maryanoff, C. A.; Maryanoff, B. *Synthetic Commun.*, 1986, *16*, 1535.
13. See Saha, M.; Muchmore, S.; van der Helm, D.; Nicholas, K. M. *J. Org. Chem.*, 1986, *51*, 1960 and references contained therein for applications of the Nicholas reaction in synthesis.
14. Fliri, H.; Mak, C. P. *J. Org. Chem.*, 1985, *50*, 3438.
15. Tsuji, J.; Takahashi, M.; Takhashi, T. *Tetrahedron Lett.*, 1980, *21*, 849.
16. Shibasaki, M.; Nishida, A.; Ikegami, S. *Tetrahedron Lett.*, 1982, *23*, 2875.
17. Two other uses of hexacarbonyldicobalt stabilized propargyl cations in stereochemical control have appearec a. Nicholas, K. M.; Siegel, J. *J. Am. Chem. Soc.*, 1985, *107*, 4999. b. Schreiber, S. L.; Sammakia, T.; Crowe, W. E. *J. Am. Chem. Soc.*, 1986, *108*, 3128.

(Received in USA 23 January 1987)