JOC*Note*

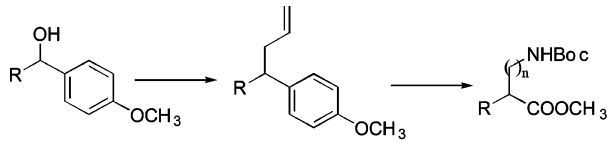
Direct C-Allylation of Aryl-Alkyl/Glycosyl Carbinols: Facile Synthesis of C-linked Carbo-β^2-/γ^2-/δ^2-Amino Acids†

Gangavaram V. M. Sharma,* Katta Laxmi Reddy, P. Sree Lakshmi, R. Ravi, and Ajit C. Kunwar

D-211, Discovery Laboratory, Organic Chemistry Division III, Indian Institute of Chemical Technology, Hyderabad 500 007, India

esmvee@iict.res.in;sharmagvm@yahoo.com

Received November 23, 2005

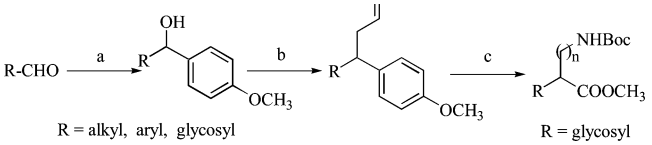


A facile $ZrCl_4$-catalyzed direct allylation of the *p*-methoxyphenyl-alkyl/glycosyl carbinols at room temperature, and the conversion of the derived aryl-glycosyl-alkenes into hitherto unknown C-linked carbo-β^2-/γ^2-/δ^2-amino acids is reported.

Introduction

Peptides play an important role in many physiological processes,[1] hence, their de novo design has emerged as a valuable tool to critically evaluate the rules of folding and structural stabilization. A variety of secondary structures have been found in β- as well as in homologous γ- and δ-peptides derived from unnatural amino acids,[2] providing a promising class of peptidomimetics. The presence of additional C atoms in β-amino acids[2] increases the structural diversity, which raises exponentially in γ- and δ-amino acids. Though β-amino acids are ubiquitous in nature, β-, γ-, and δ-peptides are not. In recent years, we have developed[3] C-linked carbo-β-amino acids (β^3-Caas) as a new class of β-amino acids and utilized them to prepare β-peptides[4] with helical diversity and robustness. During the course of our studies, we felt the imminent need to develop flexible protocols for the preparation of a variety of Caa monomers to further expand the horizon of unnatural peptides. Herein, we describe a facile $ZrCl_4$-catalyzed direct allylation of the *p*-methoxyphenyl-alkyl/glycosyl carbinols at room temperature, and the conversion of the derived *p*-methoxyphenyl-glycosyl-alkenes into hitherto unknown C-linked carbo-β^2-/γ^2-/δ^2-amino acids (Caas), wherein, the *p*-methoxyphenyl and allyl groups are envisaged as masked acid and amine functionalities, respectively.

CHART 1. General Reaction of Allylation[a]



[a] Reagents and conditions: (a) Mg, 4-bromoanisole, dry THF, reflux; (b) allyltrimethylsilane (2 equiv), $ZrCl_4$ (2 mol %), CH_3CN, rt; (c) several reagents.

The nucleophilic substitution of the hydroxy group in carbinols with allylsilane in the presence of a catalytic amount of acid under nearly neutral conditions would be a very fascinating and ideal C−C bond-forming protocol to generate aryl-alkyl/glycosyl olefins. Earlier reports on such transformations used BF_3/CH_2Cl_2,[5a] $B(C_6F_5)_3$,[5b] $InBr_3$,[5c] or $HN(SO_2F)_2$[5d] for allylation of acetates with allyltrimethylsilane, while the $InCl_3$-mediated[6] allylation of carbinols in dichloroethane was achieved on limited substrates by reacting at 80 °C for 3 h. In view of the fact that the success of the allylation process of carbinols depends on the delicate balance of cation stability and acidity of the Lewis acid, we chose a *p*-methoxyphenyl group as an aryl variant and $ZrCl_4$[7] as a new catalyst for the allylation of carbinols (Chart 1).

Results and Discussions

According to the above strategy, **1** was treated with allylsilane in the presence of $ZrCl_4$ (2 mol %) in CH_3CN at room temperature to afford **1a** (98%) in 15 min (Table 1). On the contrary, when **2** was allowed to react with allylsilane−$ZrCl_4$, no product formation was observed even after 24 h, thus asserting a mismatch between the phenyl group and the acid catalyst for carbocation formation. However, carbinol **3**,[8] with a *p*-methoxyphenyl group, reacted smoothly with allylsilane and furnished **3a** in 96% yield in 25 min. To investigate the scope and limitations of the present protocol of direct allylation of

† IICT Communication No. 050803.

(1) Nielsen, P. E. *Pseudo-peptides in Drug Discovery*; Wiley-VCH Verlag Gmbh & Co. KgaA: New York, 2004.

(2) (a) Cheng, R. P.; Gellman, S. H.; DeGrado, W. F. *Chem. Rev.* **2001**, *101*, 3219−3232. (b) Seebach, D.; Beck, A. K.; Bierbaum, D. J. *Chem. Biodiversity* **2004**, *1*, 1111−1239.

(3) Sharma, G. V. M.; Goverdhan Reddy, V.; Subhash Chander, A.; Ravinder Reddy, K. *Tetrahedron: Asymmetry* **2002**, *13*, 21−24.

(4) (a) Sharma, G. V. M.; Ravinder Reddy, K.; Radha Krishna, P.; Ravi Sankar, A.; Narsimulu, K.; Kiran Kumar, S.; Jayaprakash, P.; Jagannadh, B.; Kunwar, A. C. *J. Am. Chem. Soc.* **2003**, *125*, 13670−13671. (b) Sharma, G. V. M.; Ravinder Reddy, K.; Radha Krishna, P.; Ravi Sankar, A.; Jayaprakash, P.; Jagannadh, B.; Kunwar, A. C. *Angew. Chem.* **2004**, *116*, 4051−4055; *Angew. Chem., Int. Ed.* **2004**, *43*, 3961−3965. (c) Sharma, G. V. M.; Nagender, P.; Radha Krishna, P.; Jayaprakash, P.; Ramakrishna, K. V. S.; Kunwar, A. C. *Angew. Chem., Int. Ed.* **2005**, *44*, 6028−6032.

(5) (a) Cella, J. A. *J. Org. Chem.* **1998**, *47*, 2125−2134. (b) Rubin, M.; Gevorgyan, V. *Org. Lett.* **2001**, *3*, 2705−2707. (c) Kim, S. H.; Shin, C.; Pae, A. N.; Koh, H. Y.; Chang, M. H.; Chung, B. Y.; Cho, Y. S. *Synthesis* **2004**, 1581−1584. (d) Kaur, G.; Kaushik, M.; Trehan, S. *Tetrahedron Lett.* **1997**, *38*, 2521−2524.

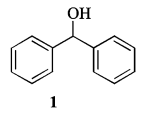
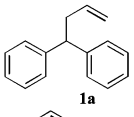
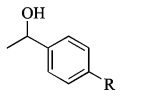
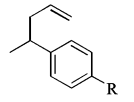
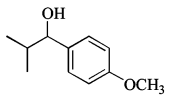
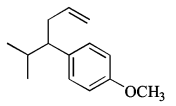
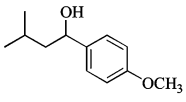
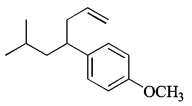
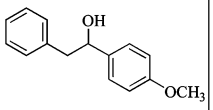
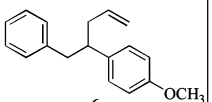
(6) (a) Yasuda, M.; Saito, T.; Ueba, M.; Baba, A. *Angew. Chem., Int. Ed.* **2004**, *43*, 1414−1416. (b) Yasuda, M.; Saito, T.; Ueba, M.; Baba, A. *Synlett* **2005**, 1737−1739.

(7) (a) Sharma, G. V. M.; Reddy, Ch. G.; Krishna, P. R. *J. Org. Chem.* **2003**, *68*, 4574−4575. (b) Sharma, G. V. M.; Goverdhan Reddy, Ch.; Radhakrishna, P. *Synlett* **2003**, 1728−1730. (c) Sharma, G. V. M.; Srinivas, B.; Radhakrishna, P. *Tetrahedron Lett.* **2003**, *44*, 4689−4691. (d) Sharma, G. V. M.; Janardhan Reddy, J.; Sree Lakshmi, P.; Radhakrishna, P. *Tetrahedron Lett.* **2004**, *45*, 6963−6965.

(8) For details, please see Supporting Information.

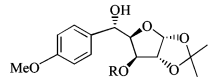
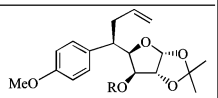
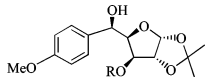
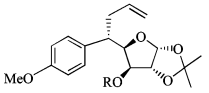
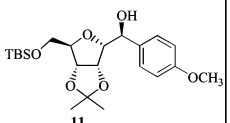
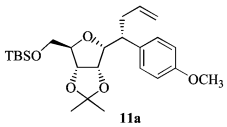
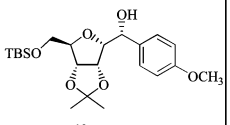
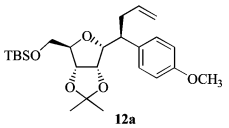
10.1021/jo052418r CCC: $33.50
Published on Web 04/12/2006

TABLE 1. $ZrCl_4$-Catalyzed Allylation of Carbinols with Allyltrimethylsilane

S.No	Carbinols	Products	Time (min)	Yield (%)
1	 **1**	 **1a**	15	98
2	 **2** R = H, **3** R = OCH_3	 **2a** R = H, **3a** R = OCH_3	[a] 25	0 96
3	 **4**	 **4a**	20	96
4	 **5**	 **5a**	30	95
5	 **6**	 **6a**	25	95

[a] No product formation was observed even after 24 h.

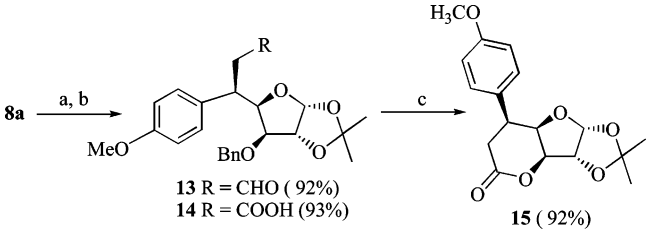
TABLE 2. $ZrCl_4$-Catalyzed Allylation of *p*-Methoxyphenyl-glycosyl Carbinols with Allyltrimethylsilane

S.NO	Carbinols	Products	Time (min)	Yield (%)
1	 **7** R = CH_3, **8** R = Bn	 **7a** R = CH_3, **8a** R = Bn	40 50	75 77
2	 **9** R = CH_3, **10** R = Bn	 **9a** R = CH_3, **10a** R = Bn	45 50	72 73
3	 **11**	 **11a**	60	65
4	 **12**	 **12a**	70	60

carbinols, **4**−**6** were prepared and subjected to a reaction with allylsilane−$ZrCl_4$ to furnish the respective olefins **4a**−**6a** (Table 1) in more than 95% yields within 20−30 min at room temperature.

Our recent interest on the synthesis of Caa containing robust peptide helices[4] prompted us to study the direct allylation of *p*-methoxyphenyl-glycosyl carbinols[8] as a novel stereoselective variant to generate new Caas. Thus, the carbinols **7** and **9** (Table 2), obtained from the known aldehyde[9a] by a Grignard reaction, were treated with allylsilane−$ZrCl_4$. They underwent facile allylation and gave the olefins **7a** and **9a**, respectively, as exclusive products having *R*′ and *S*′ configurations at the C-5 stereocenter. Olefins **7a** and **9a** displayed distinctly different

SCHEME 1. Conversion of 8a to Lactone[a]



[a] Reagents and conditions: (a) O_3, CH_2Cl_2, rt; (b) $NaClO_2$, H_2O_2, *t*-BuOH/H_2O (7:3), 0 °C−rt; (c) 10% Pd−C, EtOAc, rt.

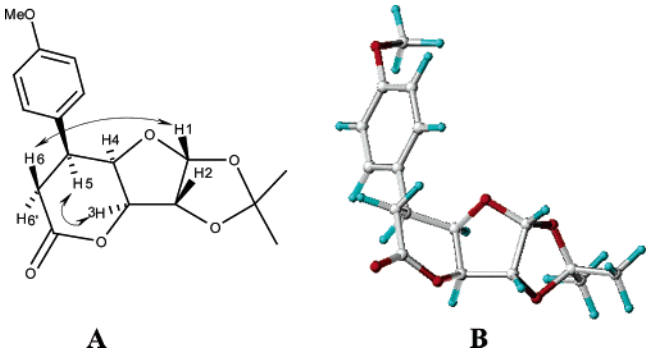


FIGURE 1. (A) Characteristic NOE of **15** and (B) energy minimization structure of **15**.

chemical shift patterns in their respective ^1H NMR spectra. Further studies on the allylation of glycosyl carbinols **11** and **12**, prepared from a known aldehyde[9b] derived from D-ribose, resulted in the exclusive formation of olefins **11a** and **12a**, respectively. Thus, the allylation method is amenable to *p*-methoxyphenyl-glycosyl carbinols with different glycosyl side chains.

To ascertain the absolute stereochemistry at the new stereocenter in the olefins **7a**, **9a**, **11a**, and **12a**, a fused lactone **15** was prepared from **8a**. Carbinols **8** and **10**,[8] on reaction with allylsilane−$ZrCl_4$, furnished **8a** and **10a** (Table 2), respectively, as exclusive products. Ozonolysis of **8a** (Scheme 1) gave the aldehyde **13** (92%), which on further oxidation afforded the acid **14** (93%). Compound **14**, on reaction with Pd−C (10%) in EtOAc, underwent debenzylation along with concomitant cyclization to give the lactone **15** (92%). The structure and the stereochemistry at the C5 stereocenter was unambiguously assigned through NMR studies.

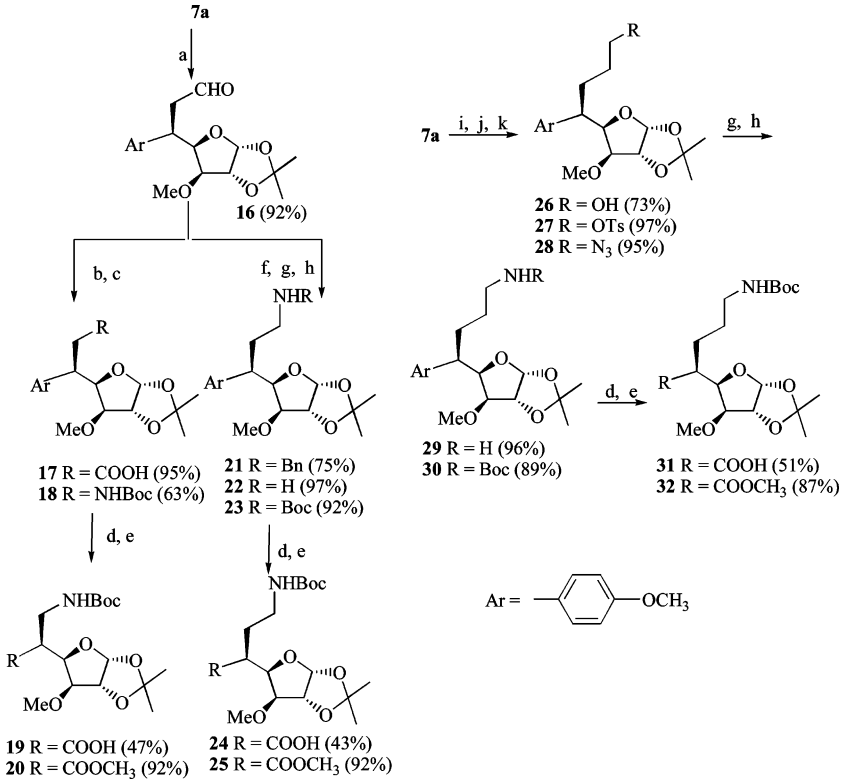
The conformational analysis of **15** (Figure 1) showed NOEs between H3/H5 and H6/H1, reflecting the presence of H-3 and H-5, similarly, H-6 and H-1 on the same face. A coupling constant of 13.7 Hz for $J_{5,6}$ suggests a dihedral angle value of about 180° for H6−C6−C5−H5. Other couplings, namely, $J_{5,6'}$ = 5.0 Hz, $J_{4,5}$ = 1.7 Hz, and $J_{3,4}$ = 2.9 Hz, supported the proposed structure. These data unequivocally proves that the configuration at C5 in **8a** is *R*. The structure was further supported by the energy minimization calculations (Figure 1) obtained from the SYBYL 6.8 program.[10]

Having successfully developed a protocol for the direct allylation of carbinols using $ZrCl_4$ as a Lewis acid, our next goal was to convert these systems into Caas with diversity.

(9) (a) Inch, T. D. *Carbohydrate Res.* **1967**, 5, 45−52. (b) Radha Krishna, P.; Ramana Reddy, V. V.; Sharma, G. V. M. *Synlett* **2003**, 1619−1622.

(10) (a) *SYBYL Force Field Manual*, version 6.6, 1999; pp 217−229. (b) Evans, J. N. S. *Biomolecular NMR Spectrocopy*, Oxford University Press: Oxford, 1995.

SCHEME 2. Conversion of 7a to Amino Acids[a]



[a] Reagents and conditions: (a) O_3, CH_2Cl_2, rt; (b) $NaClO_2$, H_2O_2, *t*-BuOH/H_2O (7:3), 0 °C−rt; (c) ClCOOEt, NaN_3, acetone, *t*-BuOH, toluene, 0 °C−reflux; (d) $RuCl_3$, $NaIO_4$, $CH_3CN/H_2O/CCl_4$ (1:1:2), 25 °C; (e) CH_2N_2, MeOH, rt; (f) $BnNH_2$, anhyd $MgSO_4$, CH_2Cl_2, $NaBH_4$, MeOH, 0 °C−rt; (g) 10% Pd−C, EtOAc, rt; (h) $(Boc)_2O$, THF, Et_3N, 0 °C−rt; (i) BH_3−DMS, dry THF, rt; (j) TsCl, Et_3N, CH_2Cl_2, 0 °C−rt; (k) NaN_3, DMF, 65 °C.

Accordingly, olefin **7a** (Scheme 2) was subjected to ozonolysis to give **16**, which on oxidation afforded the corresponding acid **17** (95%). Acid **17** on reaction with $ClCO_2Et-NaN_3$ underwent a facile Curtius rearrangement to install amine functionality and furnished **18** (63%). Similarly, **16** on reductive amination gave **21**, which on debenzylation and subsequent reaction with $(Boc)_2O$ afforded **23** (92%). Likewise, **7a** on reaction with BH_3−DMS gave alcohol **26** (73%), which on treatment with TsCl afforded **27**. Displacement of the tosyl group in **27** with NaN_3 and subsequent hydrogenation to amine **29** and protection afforded amide **30** (89%).

Thus, after the successful conversion of the olefin into amine functionality, the amides **18**, **23**, and **30** (Scheme 2) were subjected to aromatic ring oxidative cleavage[11] with $RuCl_3-NaIO_4$ at room temperature to give the corresponding acids **19**, **24**, and **31**, respectively. Finally, the acids were allowed to react with diazomethane to afford a novel class of the β^2-, γ^2-, and δ^2-Caas **20**, **25**, and **32**, respectively.

In summary, we have demonstrated a facile direct substitution of carbinols with an allyl group, thus converting a C−O bond into a C−C bond using $ZrCl_4$ (2 mol %) as a Lewis acid. A delicate balance between the Lewis acidity of $ZrCl_4$ and the carbocation-forming capability of the *p*-methoxyphenyl group is efficiently exploited to conduct the direct allylation at room temperature in short reaction times. The scope of the reaction is not restricted to the *p*-methoxyphenyl-alkyl carbinols and has been extended to other substrates. Further, it is demonstrated that the *p*-methoxyphenyl and olefinic groups act as masked acid and amine functionalities and have been effectively utilized to result in a variety of C-linked carbo-β^2, γ^2, and δ^2 classes of unnatural amino acids of significant current interest. The use of such monomers not only creates an opportunity for the design diversity but also the structural diversity, leading to the development of peptidomimetics and peptide-based drugs.

Acknowledgment. K.L.R and R.R. are thankful to UGC, and P.S.L. is thankful to CSIR, New Delhi, for financial support.

Supporting Information Available: Spectral data for all compounds along with experimental procedure. This material is available free of charge via the Internet at http://pubs.acs.org.

JO052418R

(11) Boger, D. L.; Lee, R. J.; Bounaud, P.-Y.; Meier, P. *J. Org. Chem.* **2000**, *65*, 6770−6772.