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Addition of allyltrichlorostannanes to aldehydes: application in the synthesis of 4-*N*-Boc-amino-3-hydroxy ketones

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Abstract—We wish to describe here the diastereoselective reaction between chiral *N*-Boc-α-amino aldehydes and achiral allyltrichlorostannanes leading to 1,2-*syn*-*N*-Boc-α-amino alcohols, which are treated with catalytic amounts of OsO_4 in the presence of $NaIO_4$ to provide the corresponding 4-*N*-Boc-amino-3-hydroxy ketones.

1. Introduction

Sphingolipids are a class of lipids derived from the aliphatic amino alcohol sphingosine (**1**) (Fig. 1).[1] Sphingolipids are often found in neural tissues, and play an important role in both signal transmission and cell recognition.[2,3] This diverse family of biomolecules is structurally characterized by a long carbon chain 'sphingoid' base that is derivatized with amide linked fatty acids and various polar head groups.[4] These compounds were found to possess a wide range of biological properties, being important in the chemistry of cellular membranes, cell growth differentiation and apoptosis.[5,6] The 1,2-amino alcohol moiety is present in sphingolipids, and recently, the 1-deoxy-5-hydroxy sphingosine analogues **2** and **3** have been identified as a potential new class of anticancer principles (Fig. 1).[5,6] Encouraged by this, and to provide material for further biological studies as well as access to novel analogues with potential pharmacological activities, we developed a short and efficient route for the synthesis of 4-*N*-Boc-amino-3-hydroxy ketones, which are potential precursors for the synthesis of sphingolipid derivatives. We wish to describe here the diastereoselective reaction between chiral *N*-Boc-α-amino aldehydes and achiral allyltrichlorostannanes leading to 1,2-*syn*-*N*-Boc-α-amino alcohols, which are easily converted to the corresponding 4-*N*-Boc-amino-3-hydroxy ketones.[7,8]

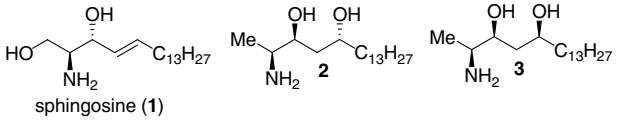

Figure 1. Sphingosine (**1**) and 1-deoxy-analogues **2** and **3**.

To our surprise, there is no general and efficient approach to 4-*N*-Boc-amino-3-hydroxy ketones described in the literature.[9]

2. Results and discussion

To prepare the corresponding allyltrichlorostannanes, the methyl esters **4** and **7** were treated with cerium(III) chloride and trimethylsilylmethylmagnesium chloride (3.0 equiv) to give an intermediate bis(trimethylsilylmethyl)carbinol which, after treatment with Amberlyst 15® resin in *n*-hexane, followed by filtration, gave allylsilanes **5** and **8** in 88% and 68% yield, respectively, for the two-step sequence (Scheme 1).[7,10]

The next step involved the reactions of allylsilanes **5** and **8** with $SnCl_4$ (Scheme 1). Allylsilanes **5** and **8** were reacted with $SnCl_4$ to promote ligand exchange, providing the corresponding allyltrichlorostannanes **6** and **9**, respectively. These reactions were followed by ^1H NMR spectroscopy.[8] For allyltrimethylsilane **5**, the ligand exchange producing allyltrichlorostannane **6** and TMSCl is complete after 60 min at room temperature (Scheme 1). Upon the addition of $SnCl_4$ to a solution of allylsilane **8** in $CDCl_3$, at 25 °C, a slightly

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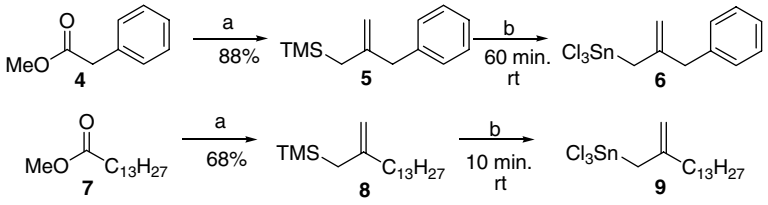
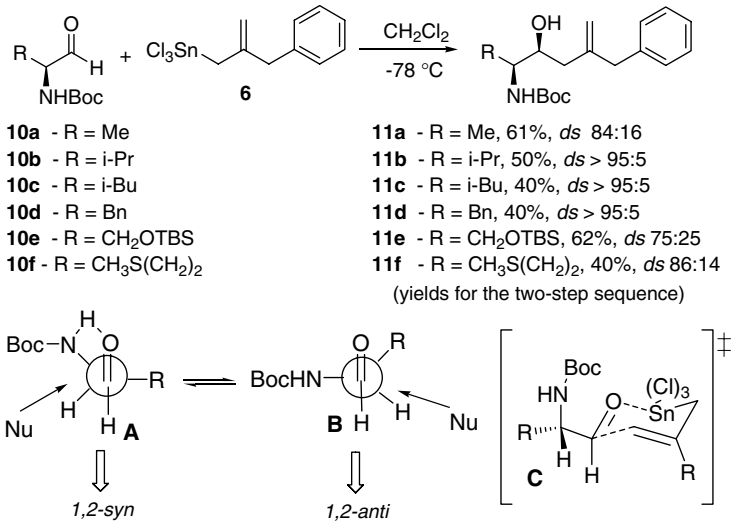


Scheme 1. Preparation of allyltrichlorostannanes **6** and **9**. Reagents and conditions: (a) (i) $CeCl_3$, $TMSCH_2MgCl$, THF, −78 °C, 18 h; (ii) Amberlyst 15, *n*-hexane, 25 °C, 3 h; (b) $SnCl_4$, CH_2Cl_2.



Scheme 2. Allyltrichlorostannane additions.

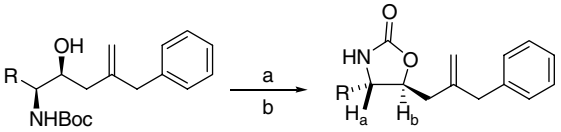
yellow homogeneous solution was obtained.[7,8] The resulting ^1H NMR spectra showed the formation of TMSCl and complete consumption of the allylsilane **8** within 10 min to give allyltrichlorostannane **9**.

We next moved to investigate the allyltrichlorostannane additions to (*S*)-*N*-Boc-α-amino aldehydes **10a–f** (Scheme 2).[7–13] Addition of aldehydes **10a–f** to a CH_2Cl_2 solution of allyltrichlorostannane **6** at −78 °C gave the 1,2-*syn*-amino alcohols **11a–f** (*anti*-Felkin addition) in good yields and with moderate to high levels of diastereoselectivity for the two-step sequence (preparation of the aldehyde and coupling with allyltrichlorostannane **6**) (Scheme 2).[14,15]

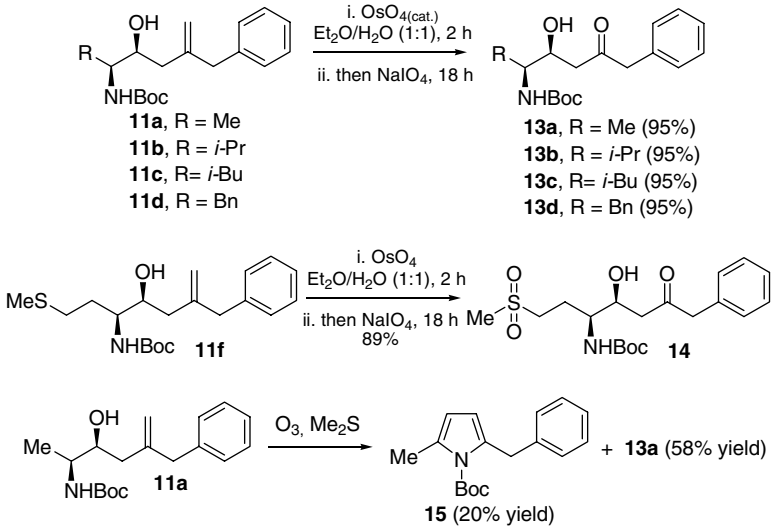
It is essential to promote the ligand exchange reaction before the addition of the aldehyde to get good yields and selectivities. This reaction benefits from the fact that the real nucleophile is the allyltrichlorostannane and not the allylsilane itself. If the allyltrichlorostannane addition reaction is carried out from −78 °C to room temperature, we have observed loss of the Boc protecting group with the corresponding deprotected homoallylic alcohols being isolated in good yields and having essentially the same selectivities.

We believe that the observed selectivity can be explained by an equilibrium between the intramolecular hydrogen bond conformer **A** and the non-bonded conformer **B** (Scheme 2). When the form **A** predominates (bulkier R groups), the *syn*-isomer is favored, whereas the prevalence of the **B**-like conformer (smaller R groups) leads to the *anti*-isomer. The nucleophile selects the less hindered *Si*-face, forming a six-member transition state **C** where the chiral residue of the aldehyde occupies a pseudo-equatorial position.

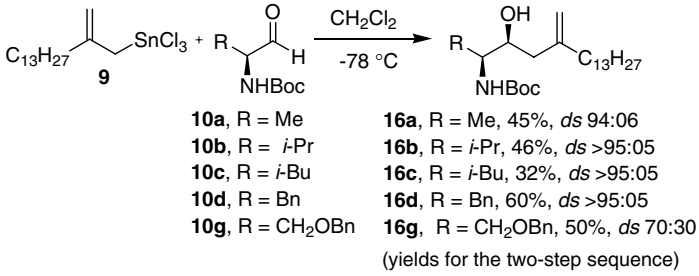
The 1,2-*syn* relative stereochemistry of the major products was unambiguously established by spectroscopic analysis of the corresponding *trans*-oxazolidinones **12b–d** (Scheme 3).[16,17] Treatment of homoallylic alcohols **11b–d** with trifluoroacetic acid (TFA) followed by cyclization with triphosgene gave **12b–d** in good yields.[16,17] Observed average coupling constants ($^3J = 4.9$ Hz for **12b**, 5.5 Hz for **12c** and 5.1 Hz for



Scheme 3. Proof of the relative stereochemistry. Reagents and conditions: (a) TFA, 1,2-ethanedithiol, rt, 50 min; (b) triphosgene, CH_2Cl_2, 0 °C, 1 h, then rt, 2 h.



Scheme 4. Synthesis of 4-*N*-Boc-amino-3-hydroxy ketones.



Scheme 5. Coupling with allyltrichlorostannane **9**.

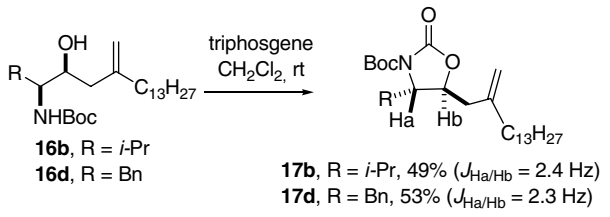
12d), upon irradiation of the hydrogens adjacent to Ha and Hb, indicated that hydrogens Ha and Hb are on the opposite faces of the heterocyclic ring, and therefore, the oxazolidinones are derived from 1,2-*syn* adducts.[16–18]

We were delighted to find that the oxidation of the homoallylic alcohols **11a–d** proceeded smoothly in the presence of osmium tetroxide (catalytic) and sodium periodate in Et_2O/H_2O to give the corresponding 4-*N*-Boc-amino-3-hydroxy ketones **13a–d** in excellent yields (Scheme 4).[9,19] It is very important to point out that, to the best of our knowledge, there is no useful and general approach to 4-*N*-Boc-amino-3-hydroxy ketones described in the literature and this methodology stands as the most efficient approach to this class of molecules.[9] Attempts to prepare the corresponding ketone from amino alcohol **11f** led to ketone **14** with concomitant oxidation to the sulfone in 89% yield (Scheme 4).

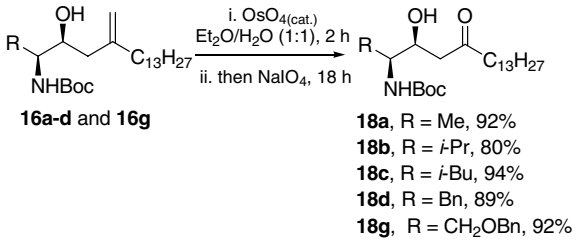
It is also important to point out that our initial attempts to promote the double bond oxidation in homoallylic alcohol **11a** by ozonolysis led to the desired product **13a** (58% yield) together with a by-product which we assigned as pyrrol derivative **15** (20% yield) (Scheme 4).[20]

We next moved to investigate the addition of allyltrichlorostannane **9** to α-aminoaldehydes (Scheme 5). The addition of allyltrichlorostannane **9** to aldehydes **10a–d** and **10g** gave adducts **16a–d** and **16g**, respectively, in good yields and with high levels of diastereoselectivity for the two-step sequence (preparation of the aldehyde and coupling with allyltrichlorostannane **9**) (Scheme 5).[15] The stereoinduction observed in these reactions again shows that the reaction favored the *anti*-Felkin product, indicating that there is an inherent selectivity toward the 1,2-*syn* product by the resident α-stereogenic center of the aldehydes.[14,15]

The relative stereochemistry was determined after the conversion of **16b** and **16d** to the corresponding *N*-Boc-oxazolidinones **17b** (49%) and **17d** (53%), respectively, by treatment of **16b**,**d** with triphosgene followed by ^{1}H NMR coupling constant analysis (Scheme 6). The observed coupling constants ($J_{Ha/Hb} = 2.4$ Hz for **17b** and 2.3 Hz for **17d**) indicates that hydrogens Ha and Hb are on opposite faces of the heterocyclic ring (Scheme 6).[16,17]



Scheme 6. Oxazolidinone formation.



Scheme 7. Synthesis of 4-*N*-Boc-amino-3-hydroxy ketones.

Treatment of homoallylic alcohols **16a–d** and **16g** with $OsO_4/NaIO_4$ gave 4-*N*-Boc-amino-3-hydroxy ketones **18a–d** and **18g** in good yields (Scheme 7).

Again, to the best of our knowledge, this is the best methodology available for the preparation of these kinds of compounds with high levels of diastereoselectivities.[19,21]

3. Conclusions

We have described here that high levels of substrate-based, 1,2-*syn*-stereocontrol could be achieved in the achiral allyltrichlorostannane addition reactions to *N*-Boc-α-amino aldehydes, leading to the *anti*-Felkin products, which were easily converted to the corresponding 4-*N*-Boc-amino-3-hydroxy ketones in good yields. This methodology stands as a new and very efficient approach to 4-*N*-Boc-amino-3-hydroxy ketones. This synthetic methodology allows compounds with programmed variations of substituents to be synthesized and is particularly important in the screening of pharmacological activity and in the study of structure-activity relationships directed toward the design of new classes of anticancer principles. Further studies in this direction are underway to explore their generality and origin and will be described in a full account of this work together with our results related to the reductions of these 4-*N*-Boc-amino-3-hydroxy ketones to the corresponding 1,3-*syn* and 1,3-*anti* diols.[21]

Acknowledgments

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References and notes

1. *Biochemistry*, 2nd ed.; Voet, D., Voet, J. G., Eds.; Wiley: New York, 1995.
2. (a) Hannun, Y. A.; Loomis, C. R.; Merrill, A. H., Jr.; Bell, R. M. *J. Biol. Chem.* **1986**, *261*, 12604; (b) Merrill, A. H., Jr.; Sereni, A. M.; Stevens, V. L.; Hannun, Y. A.; Bell, R. M., ; Kinkade, J. M., Jr. *J. Biol. Chem.* **1986**, *261*, 12610.
3. (a) Garner, P.; Park, J. M.; Malecki, E. *J. Org. Chem.* **1988**, *53*, 11061; (b) Herold, P. *Helv. Chim. Acta* **1988**, *71*, 354; (c) Nimkar, S.; Menaldino, D.; Merrill, A. H.; Liotta, D. *Tetrahedron Lett.* **1997**, *38*, 7687.
4. Menaldino, D. S.; Bushnev, A.; Sun, A.-M.; Liotta, D. C.; Symolon, H.; Desai, K.; Dillehay, D. L.; Peng, Q.; Wang, E.; Allegood, J.; Trotman-Pruett, S.; Sullards, M. C.; Merrill, A. H. *Pharmacol. Res.* **2003**, *47*, 373.
5. (a) Wiseman, J. M.; McDonald, F. E.; Liotta, D. C. *Org. Lett.* **2005**, *7*, 3155; (b) Dougherty, A. M.; McDonald, F. E.; Liotta, D. C.; Moody, S. J.; Pallas, D. C.; Pack, C. D.; Merrill, A. H., Jr. *Org. Lett.* **2006**, *8*, 649.
6. Symolon, H.; Schmelz, E. M.; Dillehay, D. L.; Merrill, A. H., Jr. *J. Nutr.* **2004**, *134*, 1157.
7. (a) Dias, L. C.; Ferreira, E. *Tetrahedron Lett.* **2001**, *42*, 7159; (b) Dias, L. C.; Ferreira, A. A.; Diaz, G. *Synlett* **2002**, 1845; (c) Dias, L. C.; Diaz, G.; Ferreira, A. A.; Meira, P. R. R.; Ferreira, E. *Synthesis* **2003**, *4*, 603; (d) Dias, L. C.; Santos, D. R.; Steil, L. J. *Tetrahedron Lett.* **2003**, *44*, 6861; (e) Dias, L. C.; Ferreira, A. A.; Santos, D. R.; Ferreira, E.; Diaz, G.; Steil, L. J.; Meira, P. R. R.; Giacomini, R. *Arkivoc* **2003**, *10*, 240.
8. Dias, L. C.; Meira, P. R. R.; Ferreira, E. *Org. Lett.* **1999**, *1*, 1335.
9. (a) Righi, G.; Ciambrone, S. *Tetrahedron Lett.* **2004**, *45*, 2103; (b) Lou, S.; Westbrook, J. A.; Schaus, S. E. *J. Am. Chem. Soc.* **2004**, *126*, 11440; (c) Machado, M. A.; Harris, M. I. N. C.; Braga, A. C. H. *J. Braz. Chem. Soc.* **2006**, *17*, 1440; (d) Zhang, Z.-W.; Hu, J.-Y. *J. Braz. Chem. Soc.* **2006**, *17*, 1447; (e) Jung, C.-K.; Krische, M. J. *J. Am. Chem. Soc.* **2006**, *128*, 17051; (f) Gennari, C.; Pain, G.; Moresca, D. *J. Org. Chem.* **1995**, *60*, 6248.
10. (a) Bunnelle, W. H.; Narayanan, B. A. *Tetrahedron Lett.* **1987**, *28*, 6261; (b) Mickelson, T. J.; Koviach, J. L.; Forsyth, C. J. *J. Org. Chem.* **1996**, *61*, 9617.
11. (a) Einhorn, J.; Einhorn, C.; Luche, J. L. *Synlett* **1991**, 37; (b) Prasad, J. V. N. V.; Rich, D. H. *Tetrahedron Lett.* **1990**, *31*, 1803.
12. (a) Fehrentz, J. A.; Castro, B. *Synthesis* **1983**, 676; (b) Golebiowski, A.; Jacobsson, U.; Jurczak, J. *Tetrahedron* **1987**, *43*, 3063; (c) Jurczak, J.; Golebiowski, A. *Chem. Rev.* **1989**, *89*, 149; (d) Stanfield, C. F.; Parker, J. E.; Kanellis, P. *J. Org. Chem.* **1981**, *46*, 4797; (e) Prasad, J. N. V. N.; Rich, D. H. *Tetrahedron Lett.* **1991**, *32*, 5857; (f) Zanatta, N.; Squizani, A. M. C.; Fantinel, L.; Nachtigall, F. M.; Borchhardt, D. M.; Bonacorso, H. G.; Martins, M. A. P. *J. Braz. Chem. Soc.* **2005**, *16*, 1255; (g) Braibante, M. E. F.; Braibante, H. T. S.; Morel, A. F.; Costa, C. C.; Lima, M. G. *J. Braz. Chem. Soc.* **2006**, *17*, 184.
13. The optical purity of aldehydes **10** was estimated to be greater than 96% ee from the ^1H NMR spectrum of the Mosher ester prepared from **10** via $NaBH_4$ reduction followed by esterification.
14. (a) Chérest, M.; Felkin, H.; Prudent, N. *Tetrahedron Lett.* **1968**, *18*, 2199; (b) Anh, N. T.; Eisenstein, O. *Nouv. J. Chem.* **1977**, *1*, 61; (c) We use the 'Felkin' descriptor to refer to the diastereomer predicted by the Felkin–Ahn paradigm. The '*anti*-Felkin' descriptor refers to diastereomers not predicted by this transition state model.
15. (a) The ratios were determined by ^1H and ^{13}C NMR spectroscopic analysis of the unpurified product mixture; (b) All of the percentage values represent data obtained from at least three individual trials.
16. Masui, Y.; Chino, N.; Sakakibara, S. *Bull. Chem. Soc. Jpn.* **1980**, *63*, 464.
17. Futagawa, S.; Inui, T.; Shiba, T. *Bull. Chem. Soc. Jpn.* **1973**, *46*, 3308.
18. Having confirmed the 1,2-*syn* relationship, the absolute stereochemistry of the newly formed hydroxyl substituent was determined by ascertaining its relationship to the known stereocenter originating from the aldehydes.

19. (a) Knorr, A.; Daub, J. *Angew. Chem., Int. Ed.* **1997**, *36*, 2817; (b) Schroeder, M. *Chem. Rev.* **1980**, *80*, 187; (c) DelMonte, A. J.; Haller, J.; Houk, K. N.; Sharpless, K. B.; Singleton, D. A.; Strassner, T.; Thomas, A. A. *J. Am. Chem. Soc.* **1997**, *119*, 9907.
20. (a) Nagafuji, P.; Cushman, M. *J. Org. Chem.* **1996**, *61*, 4999; (b) Konieczny, M.; Cushman, M. *Tetrahedron Lett.* **1992**, *33*, 6939.
21. *Homoallylic alcohols* **11** *and* **16***: general procedure*: To a solution of the corresponding allylsilane (1.5 mmol) in CH_2Cl_2 (5 mL) at rt was added $SnCl_4$ (1.1 mmol). The resulting solution was stirred at rt for 2 h and then cooled to −78 °C when a solution of aminoaldehydes (1.2 mmol) in CH_2Cl_2 (2 mL) was added. This mixture was stirred for 2 h at −78 °C and quenched by the slow addition of a satd aq solution of $NaHCO_3$ (5 mL) followed by CH_2Cl_2 (5 mL). The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (2×5 mL). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated in vacuo. Purification by flash chromatography on silica gel (30% EtOAc–hexane) gave the corresponding homoallylic alcohols **11** and **16**.