ORGANIC LETTERS

2002
Vol. 4, No. 1
47−50

Rapid and Versatile Synthesis of Functionalized Polyhydroxylated Fragments

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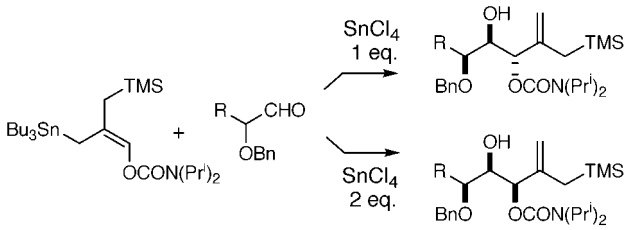
Received October 5, 2001

ABSTRACT

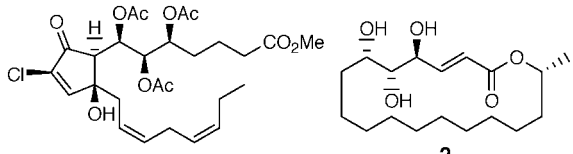


The condensation between a functionalized allylstannane and α-alkoxyaldehydes allows rapid access to complex and selectively protected trihydroxylated synthons. The stereocontrol of this process is strongly dependent upon the nature and the amount of the Lewis acid employed.

Numerous biologically active natural products contain, embedded in their often complex architectural framework, a polyhydroxylated side chain. It is therefore not surprising that the synthesis of such polyhydroxylated fragments has attracted extensive attention. Many reliable and efficient reactions discovered during this endeavor have now become fundamental tools in organic synthesis.[1] Of significant importance are the methodologies allowing the control of the relative and absolute stereochemistry of the newly formed asymmetric centers. As part of a synthetic program aimed at the efficient preparation of punaglandin[2] **1** and aspicilin[3] **2** (Scheme 1), we have explored a novel strategy for the assembly of triol substructures possessing stereocomplementary *syn-syn* and *syn-anti* relationships.

In this article, we wish to report some preliminary results in the establishment of a new and stereodivergent procedure for the construction of functionalized trihydroxylated units and their valuable transformation into polysubstituted tetrahydropyrans.

Scheme 1



During the course of some synthetic work directed toward the efficient and stereocontrolled assembly of polysubstituted tetrahydropyrans, we had the opportunity to prepare and examine the reactivity of the uniquely functionalized reagent **4**. Upon treatment with a Lewis acid, allylstannane **4** reacted with various aldehydes, affording in high yields the corresponding homoallylic alcohol **5**. Bismuth(III) triflate promoted intramolecular Sakurai cyclization (IMSC) of the resulting allylic carbamate **5** produced trisubstituted tetrahydropyran **6** (Scheme 2).[4]

Although the allylstannylation step tolerates a wide range of substitution in the aldehydes backbone, we found unex-

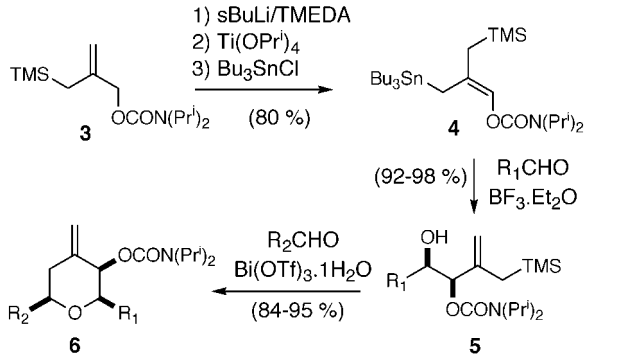
(1) For recent reviews, see: (a) Schneider, C. *Angew. Chem., Int. Ed. Engl.* **1998**, *37*, 1375. (b) Rychnovsky, S. D. *Chem. Rev.* **1995**, *95*, 2021. (c) Norcross, R. D.; Paterson, I. *Chem. Rev.* **1995**, *95*, 2041. (d) Casiraghi, G.; Zanardi, F.; Rassu, G.; Spanu, P. *Chem. Rev.* **1995**, *95*, 1677.

(2) Baker, B. J.; Okuda, R. K.; Yu, P. T. K.; Scheuer, P. J. *J. Am. Chem. Soc.* **1985**, *107*, 2976.

(3) Waanders, P. P.; Thijs, L.; Zwanenburg, B. *Tetrahedron Lett.* **1987**, *28*, 2409.

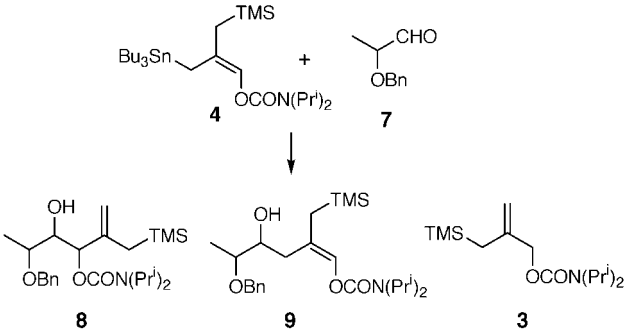
10.1021/ol016863u CCC: $22.00
Published on Web 12/15/2001

Scheme 2



pected difficulties in attempts to condense **4** with α-alkoxyaldehydes such as **7**. Instead of providing the expected homoallylic alcohol **8**, the reaction between **4** and **7**, using BF_3·Et_2O as the Lewis acid, led only to allylsilane **3** (Table 1, entry 1). Similar results were observed with $MgBr_2$ (entry

Table 1. Allylstannylation of Aldehyde **5**



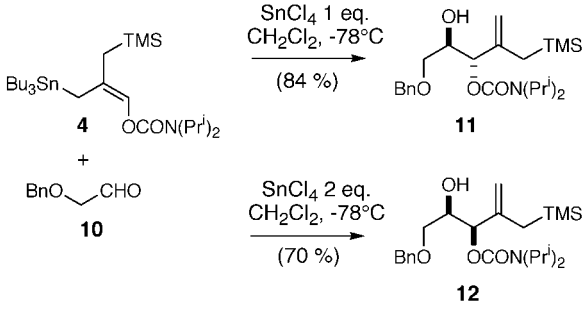
entry	conditions	product	yield (%)
1	BF_3·Et_2O, CH_2Cl_2	**3**	63
2	$MgBr_2$, CH_2Cl_2	**3**	66
3	toluene, Δ		
4	$TiCl_4$, CH_2Cl_2	**9**	63

2). Thermal conditions proved to be ineffective (entry 3), while $TiCl_4$ promoted the formation of homoallylic alcohol **9** (entry 4).[5]

Assuming that the formation of **9**, in the presence of $TiCl_4$, occurred by a transmetalation process with allylic transposition, followed by reaction of the resulting allyltitanium intermediate with **7**, we envisioned to take advantage of such a process to open an access to homoallylic alcohol **8**. Since there have been numerous reports of transmetalations involving tin halides based Lewis acids, we decided to carry out our reactions using $SnCl_4$.[6]

After a broad screening of the reaction conditions, we were pleased to find that the treatment of allylstannane **4** with 1 equiv of $SnCl_4$ followed, after a period of equilibration, by the addition of α-benzyloxyacetaldehyde **10** led very efficiently to compound **11**. This homoallylic alcohol was isolated as a single diastereoisomer, which was assigned the *anti* relative stereochemistry (Scheme 3). In sharp contrast,

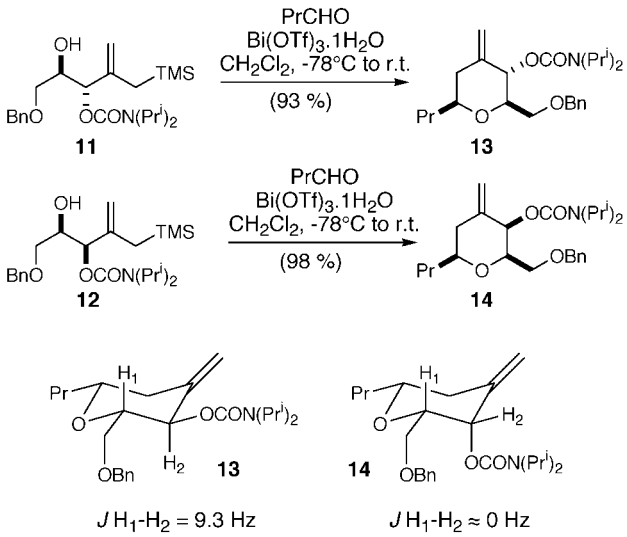
Scheme 3



the use of 2 equiv of $SnCl_4$ spectacularly reversed the stereoselectivity in favor of the *syn* adduct **12**.[7] It is noteworthy that, in these compounds, all three hydroxyl functions are differentiated.

To establish the stereochemistry of **11** and **12** and to illustrate some of their synthetic utility, both homoallylic alcohols were engaged in Bi(III) triflate promoted IMSC condensation with butyraldehyde to furnish in high yields the stereocomplementary tetrahydropyrans **13** and **14** (Scheme 4). It is noteworthy that in **13** the carbamate function occupies

Scheme 4



an equatorial position, whereas it is axially disposed in **14**. The unambiguous assignment of the stereochemistry of these

(4) Leroy, B.; Markó, I. E. *Tetrahedron Lett.* in press. For a related approach, see: Markó, I. E.; Leroy, B. *Tetrahedron Lett.* **2000**, *41*, 7225.

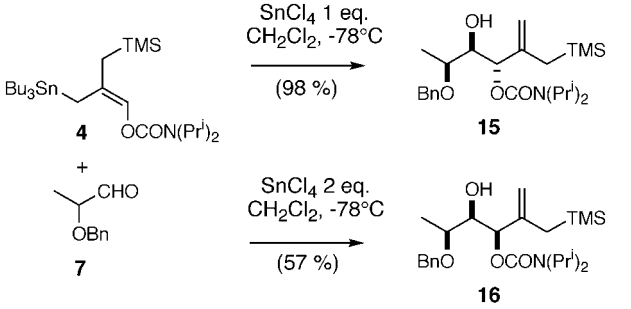
(5) Similar results have been obtained for other allylstannane-carbamate compounds. Krämer, T.; Schwark, J.-R.; Hoppe, D. *Tetrahedron Lett.* **1989**, *30*, 7037.

(6) (a) Thomas, E. J. *J. Chem. Soc., Chem. Commun.* **1997**, 411. (b) Yamamoto, Y.; Asao, N. *Chem. Rev.* **1993**, *93*, 2207. (c) Marshall, J. A. *Chem. Rev.* **1996**, *96*, 31.

heterocycles proved to be a reliable procedure for determining the stereochemistry of the starting alcohols.[8]

To broaden the scope of this new methodology, we examined the possibility of introducing selectively a third stereocenter in the condensation product. Thus, α-benzyloxypropionaldehyde **7** was reacted with **4** in the presence of various amounts of $SnCl_4$. Remarkably, this condensation, mediated by 1 equiv of $SnCl_4$, afforded, in essentially quantitative yield, diastereomerically pure alcohol **15**. Subsequent transformations (vide infra) revealed that **15** possessed the *syn-anti* relative stereochemistry, as shown in Scheme 5. In agreement with our previously mentioned

Scheme 5

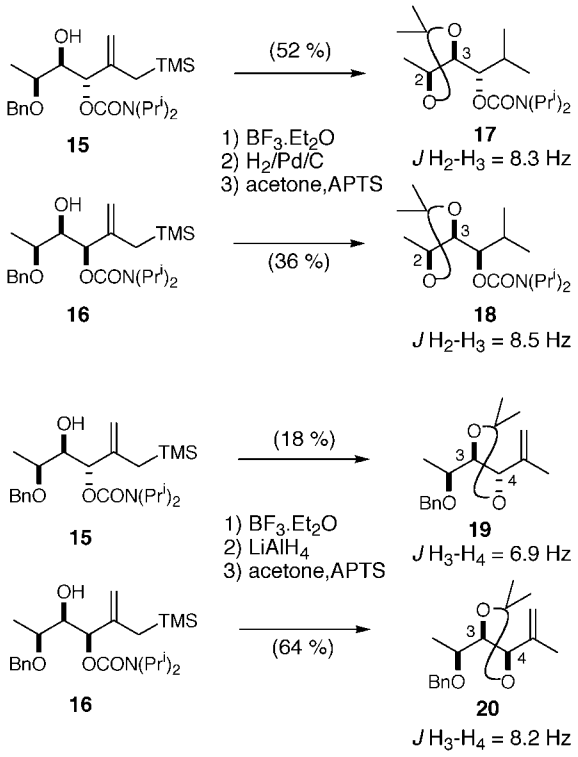


observations, the use of 2 equiv of $SnCl_4$ led to a complete reversal in the stereochemistry of the 3,4-diol substituents and only the *syn-syn* stereoisomer **16** was isolated.

The determination of the stereochemical relationships in **15** and **16** was carried out via the formation of acetonide derivatives for each pair of diol functions, as depicted in Scheme 6. Initial desilylative treatment of **15** and **16** with $BF_3{\cdot}Et_2O$, followed by chemoselective removal of the benzyl protecting group and concomitant alkene reduction using H_2 and Pd/C, afforded the corresponding 2,3-diols. Acetalization of these diols furnished the desired acetonides **17** and **18,** respectively. On the other hand, chemoselective reductive cleavage of the carbamate function and acetalization gave access to compounds **19** and **20**. The value of the coupling constant between O-vicinal hydrogens in these four acetonides revealed three *syn* relationships (characterized by a ^3J of around 8.4 Hz) and one *anti* (with a coupling constant of 6.9 Hz).[9]

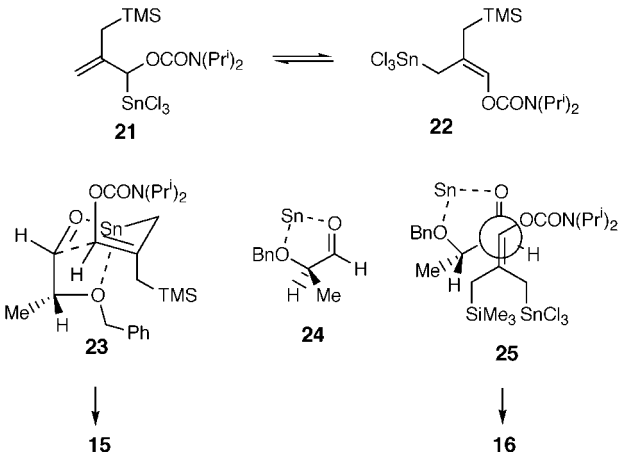
To rationalize the observed variation of stereoselectivity as a function of the quantity of Lewis acid employed, we need to take into account the structure and reactivity of the various allyltin species present in the reaction mixture (Scheme 7). Previous studies have revealed that addition of

Scheme 6



$SnCl_4$ (as well as several other Lewis acids) to allylstannane reagents resulted in the formation of organotin trichloride derivatives with concomitant 1,2-migration of the allylic C−C double bond. In analogy with these observations, we believe that, in the case of allylstannane **4**, transmetalation takes place to generate initially the α-stannylated carbamate **21**. Rapid equilibration toward the sterically less hindered and probably more reactive tin species can then occur, affording vinylcarbamate **22**. Addition of an α-alkoxyaldehyde would then lead to the allylation products **15** or **16**,

Scheme 7. Chloride Ligands on Tin Have Been Removed for Reasons of Clarity



Chloride ligands on tin have been removed for reasons of clarity.

(7) The stoichiometry of the Lewis acids employed in transmetalation processes appears to be often an underestimated factor in the control of the selectivity of such allylmetalation reactions. Few studies take that parameter into account. See: Yamamoto, Y.; Taniguchi, K.; Maruyama, K. *J. Chem. Soc., Chem. Commun.* **1985**, 1429.

(8) Determined inter alia by analysis of the coupling constants in ^1H NMR and comparison with similar compounds of known relative stereochemistry (see ref 2).

(9) Allevi, P.; Tarocco, G.; Longo, A.; Anastasia, M.; Cajone, F. *Tetrahedron: Asymmetry* **1997**, *8*, 1315.

depending upon the amount of $SnCl_4$ employed. When 1 equiv of $SnCl_4$ is used, coordination of both the aldehyde carbonyl and the benzyloxy oxygen to tin leads to a chelated intermediate akin to **23** (the carbamate function might also be involved to some extend in the coordination to tin, though it is not required). Addition of the allylic species onto the aldehyde then occurs in a Cram-chelated mode, via the transition state **23**. When 2 equiv of $SnCl_4$ are employed, transmetalation occurs with the first equivalent to generate **22**. The second equivalent serves to form the chelated α-alkoxyaldehyde **24**. We believe that the absence of available basic lone-pairs (sequestered by the coordination to $SnCl_4$) would preclude the passage via a Zimmerman−Traxler-type transition state and favor instead an open transition state such as **25**.[10]

In summary, we have developed a simple and stereocontrolled access to trihydroxylated fragments in a stereodivergent manner. These units are useful building blocks for the synthesis of functionalized tetrahydropyrans and polyhydroxylated fragments present in a wide range of biologically active natural products. Current studies are now directed toward delineating the full scope of this novel methodology, transforming these fragments into more elaborated polyol chains, and applying this approach to the total synthesis of complex natural products. The results of these investigations will be reported in due course.

(10) For an extensive study on the addition of allylstannanes onto alkoxyaldehydes and the importance of chelation, see: (a) Almendros, P.; Thomas, E. J. *J. Chem. Soc., Perkin Trans. 1* **1997**, 2561. (b) Hallett, D. J.; Thomas, E. J. *Synlett* **1994**, 87.

Acknowledgment. Financial support of this work by the Université catholique de Louvain, the Actions de Recherche Concertées (convention 96/01-197), the Fonds pour la Recherche dans l'Industrie et l'Agriculture (FRIA) and the Fonds de la Recherche Fondamentale Collective (dossier no. 2.4571.98) is gratefully acknowledged. I.E.M. is thankful to Merck & Co. for its continuous support and for receiving the Merck Young Investigator Award.

Supporting Information Available: Experimental procedures and characterization for compounds **11**−**16**. This material is available free of charge via the Internet at http://pubs.acs.org.

OL016863U