ORGANIC LETTERS

2006
Vol. 8, No. 20
4649−4652

Stereoselective Synthesis of 2,4,5-Trisubstituted Tetrahydropyrans Using an Intramolecular Allylation Strategy

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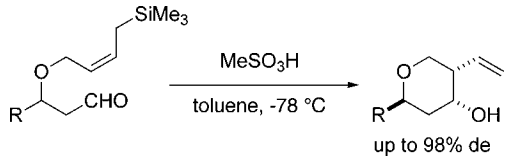
Received August 8, 2006

ABSTRACT



A highly stereoselective route to 2,4,5-trisubstituted tetrahydropyrans is reported. The key step employs an intramolecular allylation of a (*Z*)-allylsilane onto an aldehyde under Brønsted acid activation. Complete 1,4-stereoinduction accounts for the formation of only two out of the possible four THP products. The level of 1,3-stereoinduction is optimal when the reaction is carried out in an apolar solvent, which is in accord with electrostatics being key to controlling this aspect of the stereoselectivity.

Substituted tetrahydropyrans (THPs) are important targets because of their frequent occurrence in natural products and medicinally important molecules.[1] They have been constructed in a wide variety of ways, with the most common strategies involving cyclizations onto oxacarbenium ions or epoxides, hetero Diels−Alder cyclizations, conjugate addition reactions, and the reduction of cyclic hemiketals.[1] Of the range of permutations that is available for trisubstituted THPs, the 2,4,6-substitution pattern has been the most widely studied; indeed, excellent methods now exist for its construction.[1,2] In sharp contrast, stereoselective approaches to 2,4,5-trisubstituted THPs remain rare.[3] A particularly attractive route to this substitution pattern was recently described by Willis and co-workers (Scheme 1, eq 1).[3b] In their approach, a Prins-type cyclization between an alkene and an oxacarbenium ion, generated in situ from MEM ether **1**, provided the 2,4,5-trisubstituted THP **2** in which all three substituents occupy equatorial positions. In an alternative approach, Schmidt employed a completely regio- and stereoselective ring-opening reaction on epoxide **3** to generate the diastereoisomeric 2,4,5-trisubstituted THP **4** (Scheme 1, eq 2).[3d]

We now wish to report a new approach to 2,4,5-trisubstituted THPs, which is complementary in its stereochemical outcome to the methods of both Schmidt and Willis. To serve as an introduction, we have recently been investigating intramolecular allylation strategies in which an allylsilane nucleophile is covalently attached to an aldehyde electrophile through a temporary silicon connection.[4,5] In the case of aldehyde **5**, the allylsilane nucleophilic component was readily tethered to the aldehyde electrophile through its

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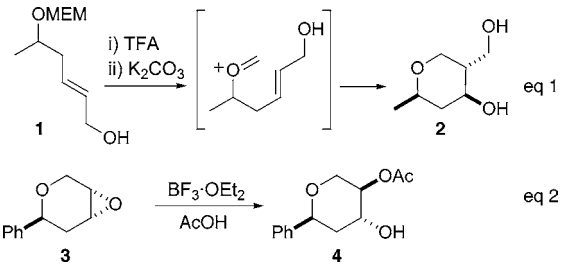
(3) (a) Kulesza, A.; Ebetino, F. H.; Mishra, R. K.; Cross-Doersen, D.; Mazur, A. W. *Org. Lett.* **2003**, *5*, 1163. (b) Al-Mutairi, E. H.; Crosby, S. R.; Darzi, J.; Harding, J. R.; Hughes, R. A.; King, C. D.; Simpson, T. J.; Smith, R. W.; Willis, C. L. *Chem. Commun.* **2001**, 835. (c) Angle, S. R.; El-Said, N. A. *J. Am. Chem. Soc.* **1999**, *121*, 10211. (d) Schmidt, B. *J. Chem. Soc., Perkin Trans. 1* **1999**, 2627. (e) Kay, I. T.; Bartholomew, D. *Tetrahedron Lett.* **1984**, *25*, 2035.

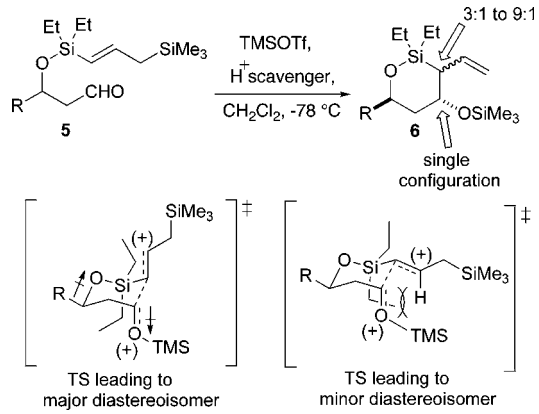
10.1021/ol061957v CCC: $33.50
Published on Web 09/02/2006

Scheme 1. Existing Stereoselective Approaches to 2,4,5-Trisubstituted THPs



β-carbinol stereocenter. Treatment of **5** with TMSOTf, in the presence of a Brønsted acid scavenger, effected intramolecular allylation to provide two out of the four possible oxasilacycles **6** (Scheme 2).[4c] Complete 1,3-stereoinduction

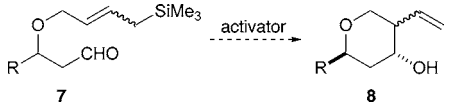
Scheme 2. Intramolecular Allylation of Aldehyde **5** Generates Two Out of the Possible Four Oxasilacycles



is observed in this cyclization. We have rationalized this observation on electrostatic grounds according to a modified Evans dipole model in which the dipole moments across the polar C=O and C−O bonds are opposing one another in the transition state (TS).[6] The more modest 1,4-stereoinduction arises from minimizing steric interactions between the allylsilane and the ethyl substituents contained within the silyl tether, which is best achieved by placing the allylsilane in a pseudoaxial orientation.

Substituting the diethylsilyl tether in aldehyde **5** for a methylene group would provide **7** and a route to the corresponding 2,4,5-trisubstituted THP **8** (Scheme 3).[3] On the basis of our previous observations with **5** (Scheme 2),[4c]

Scheme 3. Intramolecular Allylation Approach to 2,4,5-Trisubstituted THPs **8**



we hypothesized that this structural change might have a pronounced effect on the 1,4-stereoinduction but would have minimal impact on the 1,3-stereoinduction because the electrostatic interactions governing this aspect of the reaction should effectively remain the same. Furthermore, by using a more robust methylene bridge to connect the allylsilane to the aldehyde, we hoped to be able to investigate Brønsted acid activators, something we had been unable to do in our previous cyclizations because of the lability of the silyl tether to these activators.

Because β-hydroxy esters are readily accessed in enantiomerically enriched form,[7] we opted for a route to the cyclization precursor **7** which would exploit this facile entry into enantiomerically enriched systems (Table 1). The lynchpin step in our synthesis of **7** would therefore involve the formation of the ether linkage between β-hydroxy ester **11** and an allylsilane or a masked synthetic equivalent. Mindful of the propensity for allylsilanes containing a leaving group at the γ-terminus to degrade through a vinylogous Si-mediated elimination sequence,[8] we chose to tether a propargyl silane precursor instead, as we expected this functionality would be less susceptible to degradation via this pathway. Significantly, unmasking the double bond at a later stage in the synthesis through a partial hydrogenation would also allow access to a (*Z*)-allylsilane, which has been shown in related systems to impart higher levels of stereoselectivity in intramolecular allylation reactions than its (*E*)-stereoisomer.[9]

The propensity for β-hydroxy esters to undergo dehydration or a retro-aldol transformation called for a nonbasic etherification procedure. To this end, propargyl alcohol **9**[10] was first transformed into trichloroacetimidate **10**,[11] which reacted with β-hydroxy ester **11**, in the presence of TMSOTf, to provide ether **12** in good yield.[12] Partial hydrogenation of the alkyne functionality in **12** using Ra−Ni/H_2 afforded the

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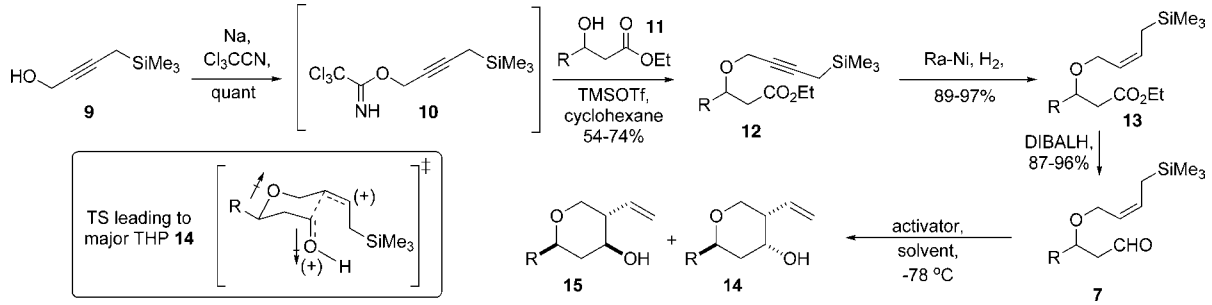
(12) Standard etherification conditions using trichloroacetimidates use TfOH as the activator. In our case, however, this acid effected protodesilylation of ether **12**, providing an allene as the major product.

Table 1. Stereoselective Synthesis of 2,4,5-Trisubstituted THPs



entry[a]	aldehyde 7	R	solvent	activator	time (min)	ratio[b] 14/15	isolated yield[c] 14 (%)
1	**7a**	Ph	CH_2Cl_2	TMSOTf	1.5	12:1	81
2	**7a**	Ph	$MeCN/CH_2Cl_2$ 1:1	TMSOTf	1.5	5:1	73
3	**7a**	Ph	CH_2Cl_2	$MeSO_3H$	1.5	30:1	86
4	**7a**	Ph	toluene	$MeSO_3H$	45	>50:1	88
5	**7b**	^{n}Bu	toluene	$MeSO_3H$	50	50:1	91
6	**7c**	^{i}Bu	toluene	$MeSO_3H$	40	32:1	87
7	**7d**	Me	toluene	$MeSO_3H$	45	7:1	82
8	**7e**	$BnOCH_2CH_2-$	toluene	$MeSO_3H$	40	12:1	81
9	**7f**	$TBDPSOCH_2-$	toluene	$MeSO_3H$	40	18:1	82
10	**7g**	2-furyl	toluene	$MeSO_3H$	40	25:1	86
11	**7h**	(*E*)-styryl	toluene	$MeSO_3H$	40	19:1	84

[a] Reaction conditions: activator (1.1 equiv), TTBP (1.2 equiv with TMSOTf only), −78 °C. [b] Ratio calculated from analysis of the crude reaction mixture by ^{1}H NMR. [c] Isolated yields following column chromatography.

desired allylsilane **13**.[13] Finally, DIBALH reduction of the ester group in **13** proceeded uneventfully to afford the corresponding aldehyde cyclization precursor **7**.

Commencing our intramolecular allylation study with the conditions that had proved so successful in our earlier work,[4] we treated aldehyde **7a** with TMSOTf in CH_2Cl_2 at −78 °C in the presence of the Brønsted acid scavenger tri-*tert*-butyl pyrimidine (TTBP). Intramolecular allylation proceeded smoothly, providing two of the possible four hydroxy-substituted THPs **14a** and **15a** in a ratio of 12:1 (Table 1, entry 1).[14] The relative stereochemistry of the major diastereoisomer **14a** was elucidated by nOe experiments and vicinal coupling constant measurements.[15] Final corroboration came from an X-ray structure, which also showed that the ring adopts a standard chair conformation (see Supporting Information). The stereochemistry of the minor diastereoisomer **15a** was elucidated from vicinal coupling constant data.[15]

The stereochemical outcome of this intramolecular allylation was in contrast to our previous work (Scheme 2). This time, complete 1,4-stereoinduction was observed, with both diastereoisomers now resulting from TSs in which the allylsilane adopts a pseudoequatorial position in a chairlike TS, an orientation which had been disfavored in our silyl-tethered allylations. We propose that this reversal in 1,4-stereoinduction can be explained by the absence of steric clashes between the allylsilane and the methylene bridge now favoring this diastereoisomeric TS (cf. TSs in Scheme 2 and the TS in Table 1, inset). The minor diastereoisomer now derives from an erosion in the 1,3-stereoinduction, although it is important to note that the sense of 1,3-induction is in complete agreement with our earlier work, as had been predicted. We postulate that its attenuation results from a steric interaction between the pseudoaxial aldehyde and the now pseudoequatorial allylsilane in the reacting TS, a situation which is worsened by the (*Z*)-stereochemistry of the allylsilane. Postulating that replacing the Lewis acid activator for a Brønsted acid would relieve these interactions and help recover the 1,3-induction, it was gratifying to observe that switching from TMSOTf to $MeSO_3H$,[9b] led to an increase in the stereoselectivity to 30:1 (**14a**/**15a**) (Table 1, entry 3).

A number of factors may be responsible for the aldehyde preferring to adopt a pseudoaxial orientation in the favored TS. Such a conformation, in association with the use of a (*Z*)-allylsilane, would concur with a degree of secondary frontier molecular orbital control, as proposed by Keck and Denmark,[9b,16] which is only possible if the reacting groups adopt such a syn synclinal orientation. However, we were keen to assess the importance of our proposed dipole

(13) *E*)/(*Z*) ratio of **13** = 95:5. This reaction had to be monitored carefully to avoid overreduction.

(14) The two diastereoisomers were readily separated by flash column chromatography. Loss of the TMS group under the reaction conditions meant that the products were obtained as the free alcohol.

(15) See Supporting Information for a full analysis.

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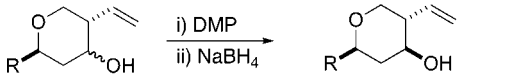
minimization model,[4c,6] by carrying out the reaction in solvents of different polarities. In line with electrostatics being a controlling factor, cyclization of **7a** in a 1:1 MeCN/CH_2Cl_2 mix, and using a TMSOTf activator, led to a significant reduction in the 1,3-stereoinduction (**14a**/**15a**, 5:1, Table 1, entry 2). From this result, we reasoned that using a Brønsted acid alongside an apolar solvent would provide the optimum conditions for this transformation, which indeed proved to be the case: reaction of **7a** with $MeSO_3H$ in toluene at −78 °C provided a quantitative yield of THPs **14a** and **15a**, this time in a >50:1 ratio, although now the reaction time was increased from 90 s to 45 min (Table 1, entry 4). The generality of the reaction under these optimized conditions was demonstrated with a range of aldehydes (Table 1). All those tested reacted similarly, with the methyl-substituted system providing the lowest, although still good, stereoselectivity.

In line with the two diastereoisomeric products being epimeric at the carbinol center, Dess−Martin oxidation of the crude cyclization products **14**/**15a** and **14**/**15b**, obtained from **7a** and **7b**, respectively, in both cases effected stereoconvergence of the mixture to a single ketone product in quantitative yield. Usefully, this keto functionality could then be reduced to the corresponding THP **15** with excellent stereoselectivity using $NaBH_4$. Axial hydride attack accounts for the formation of what was the minor THP diastereoisomer from our intramolecular allylation (Scheme 4).[17]

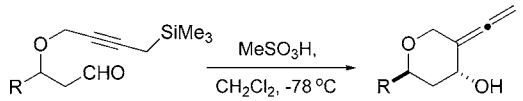
Scheme 4. Two-Step Epimerization of the 4-Hydroxyl Group



15a R = Ph, 87%, dr >99:<1
15b R = ^{n}Bu, 83%, dr 15:1

Because a propargylsilane **12** is an intermediate in the synthesis of cyclization precursor **7**, we were keen to investigate whether such a pendant nucleophile might cyclize onto an aldehyde to produce an allene-containing THP.[4a,18] To this end, DIBALH reduction of ester **12b** proceeded uneventfully to provide aldehyde **16b**. Cyclization under our optimized allylation conditions, however, was slow (40 min) and led to a range of products, including the desired allene **17b** in 56% yield. Suspecting the slower rate of reaction was allowing other reaction pathways to be followed, we returned to CH_2Cl_2 as solvent and with this change were pleased to obtain an 83% yield of the desired allene **17b** as a 10:1 mixture of diastereoisomers (relative stereochemistry of major diastereoisomer in line with our previous observations) (Scheme 5). Aldehyde **16a** possessing a Ph substituent reacted with even better stereoinduction, with allene **17a** now being obtained as a single diastereoisomer (88%).

Scheme 5. Stereoselective Synthesis of Allene-Containing THPs



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17a R = Ph, 88%, dr >99:<1
17b R = ^{n}Bu, 83%, dr 10:1

In summary, a highly stereoselective route to 2,4,5-trisubstituted THPs has been developed. The key step involves an intramolecular allylation of a (*Z*)-allylsilane onto an aldehyde under Brønsted acid activation. Complete 1,4-stereoinduction accounts for the formation of only two out of the possible four THP products. The level of 1,3-stereoinduction is optimal when the reaction is carried out in an apolar solvent, which is in accord with electrostatics being key to controlling the sense of 1,3-induction. Significantly, the observed relative stereochemistry of the major diastereoisomer is complementary to 2,4,5-trisubstituted THPs prepared by alternative methods. The strategy is readily modified to provide different product outcomes. Thus, an oxidation−reduction sequence on THP **14** provides an efficient route to the all-equatorial product **15**, whereas substituting the allylsilane nucleophile for a propargylsilane allows the formation of a versatile allene-containing THP **17**, again with high stereoselectivity. Future work will focus on extending this cyclization strategy to the preparation of other oxygen heterocycles.

Acknowledgment. We are grateful to the University of Birmingham and the EPSRC for a studentship to P.J.J.

Supporting Information Available: General experimental procedures and characterization data for all new compounds and an X-ray crystallographic file (in CIF format) for compound **14a**. This material is available free of charge via the Internet at http://pubs.acs.org.

OL061957V

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