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Stereoselective Synthesis of 4-Hydroxy-2,3,6-trisubstituted Tetrahydropyrans

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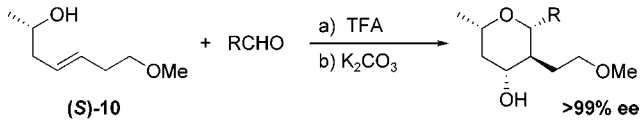
ABSTRACT



Reaction of homoallylic alcohols with aldehydes in the presence of TFA gives, after hydrolysis of the ester, 4-hydroxy-2,3,6-trisubstituted tetrahydropyrans with the creation of three new stereocenters in a single-pot process. By varying the aldehyde component, a variety of functionalized side chains are installed at C-2. The utility of this approach is extended to the enantioselective synthesis of tetrahydropyrans with >99% ee.

Substituted tetrahydropyrans are common structural features of many natural products, and some such as polycavernoside A possess substituents at C-2, C-3, C-4, and C-6, all in an equatorial position.[1] Several approaches to the synthesis of the core of such heterocycles have been reported.[2]

A strategy that is gaining importance for the stereoselective synthesis of tetrahydropyrans is the acid-promoted Prins-type reaction involving cyclization of an oxycarbenium ion generated in situ either from reaction of the parent homoallylic alcohol with an aldehyde or from a homoallylic acetal[3] or α-acetoxy ether.[4] Such reactions have been widely used for the construction of di- and trisubstituted tetrahydropyrans;[5] however, there have been few reports of this approach being applied to the creation of more complex substitution patterns. Notable examples include the work of Rychnovsky and co-workers[6] involving conversion of 4-allyl-1,4-dioxanes to 4-chloro-2,3,6-trisubstituted tetrahydropyrans in good yield. This methodology was extended to the synthesis of the pentasubstituted tetrahydropyran fragment of phorboxazole A by the $BF_3{\cdot}OEt_2$-mediated cyclization of an α-acetoxy ether.[7] We now report our investigations leading to a flexible and efficient approach to the stereocontrolled synthesis of 4-hydroxy-2,3,6-trisubstituted tetrahydropyrans from homoallylic alcohols and aldehydes with the creation of three new stereocenters in a single-pot process.

We have already shown that under acidic conditions, homoallylic acetal **1** can be converted to 2,4,5-trisubstituted tetrahydropyrans **2** in good yield and with excellent stereocontrol, all substituents being in an equatorial position

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(1) (a) Yamashita, M.-Y.; Haddock, R. L.; Yasumoto, T. *J. Am. Chem. Soc.* **1993**, *115*, 1147. (b) Yamashita, M.-Y.; Seki, T.; Paul, V. J.; Naoki, H.; Yasumoto, T. *Tetrahedron Lett.* **1995**, *36*, 5563.

(2) (a) Markó, I. E.; Dumeunier, R.; Leclerq, C.; Lero, B.; Plancher, J.-M.; Mekhalfia, A.; Bayston, D. J. *Synthesis* **2002**, 958. (b) Elliot, M. C. *J. Chem. Soc., Perkin Trans. 1* **2002**, 2301.

(3) See for example: (a) Zhang, W.-C.; Viswanathan, G. S.; Li, C. J. *Chem Commun*. **1999**, 291. (b) Semeyn, C.; Blaauw, R. H.; Speckamp, W. N. *J. Org. Chem*. **1997**, *62*, 3426. (c) Loh, T.-P.; Hu, Q.-Y.; Ma, L.-T. *J. Am. Chem Soc*. **2001**, *123*, 2450.

(4) See for example: (a) Dahanukar, V. H.; Rychnovsky, S. D. *J. Org. Chem*. **1996**, *61*, 8317. (b) Kopecky, D. J.; Rychnovsky, S. D. *J. Org. Chem*. **2000**, *65*, 191.

(5) For example: (a) Cloninger, M. J.; Overman, L. E. *J. Am. Chem. Soc.* **1999**, *121*, 1092. (b) Yang, J.; Viswanathan, G. S.; Li, C.-J. *Tetrahedron Lett.* **1999**, *40*, 1627. (c) Rychnovsky, S. D.; Hu, Y.; Ellsworth, B. *Tetrahedron Lett.* **1998**, *39*, 7271. (d) Markó, I. E.; Chellé, F. *Tetrahedron Lett.* **1997**, *38*, 2895.

(6) Rychnovsky, S. D.; Marumoto, S.; Jaber, J. J. *Org. Lett.* **2001**, *3*, 3815.

(7) Rychnovsky, S. D.; Thomas, C. R. *Org. Lett.* **2000**, *2*, 1217.

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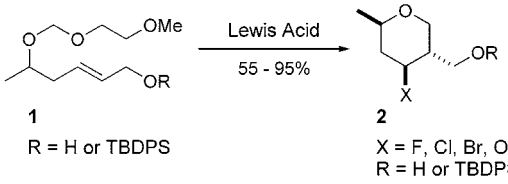
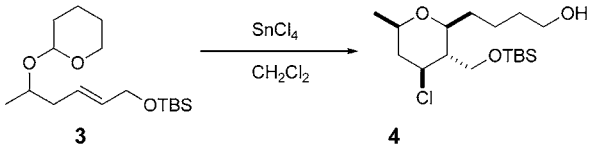
Scheme 1. Cyclization of Homoallylic Acetals



(Scheme 1).[8] By judicious choice of reaction conditions, the group at C-4 can be either a halide, ester, or acetamide. It was envisaged that if a tetrahydropyranyl (THP)- rather than MEM-protected alcohol were used in the acid-mediated cyclization, then a tetrasubstituted tetrahydropyran would be formed (Scheme 2).[9] Thus, the THP-protected (*E*)-homo-

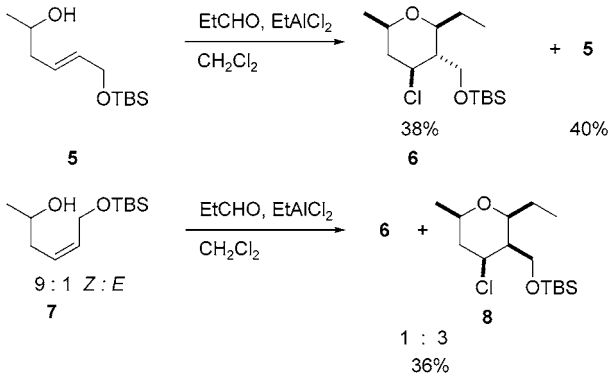
Scheme 2. Cyclization of **3**



allylic alcohol **3** was treated with $SnCl_4$,[10] giving the heterocycle **4** with all substituents in an equatorial position as apparent from the ^{1}H NMR spectrum cf. δ 4.22 (ddd, J = 11.9, 10. 8, 4.8 Hz, 4-H) and δ 2.21 (ddd, J = 12.8, 4.8, 1.8 Hz, 5-Heq).

Unfortunately, the yield of **4** was less than 50% and so this approach was abandoned in favor of the in situ formation of the intermediate oxycarbenium ion from reaction of a homoallylic alcohol with an aldehyde (Scheme 3).

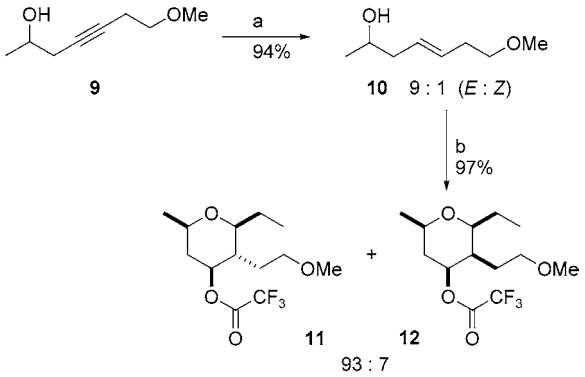
Scheme 3. Cyclization of (*E*)- and (*Z*)-Homoallylic Alcohols



This strategy has the advantage of being very flexible; by judicious choice of the appropriate aldehyde, a range of functionalized side-chains can be installed at C-2 of the tetrahydropyran in a single-pot process.[11] The stereochemical outcome of the reaction was first explored using both (*E*)- and (*Z*)-alkenes **5** and **7**. Thus, treatment of the (*E*)-homoallylic alcohol **5** with ethyl aluminum dichloride and propanal gave 4-chloro-2,3,6-trisubstituted tetrahydropyran **6** with all substituents in the equatorial position. In contrast, treatment of the (*Z*)-homoallylic alcohol **7** under similar conditions gave diastereomers **8** and **6** in a 3:1 ratio. The structure of **8** was confirmed by NOE studies, which clearly revealed that the substituent at C-3 was axial, by an enhancement (5.9%) between 5-H_{ax} and the 3-CH_2. These results are in accord with those of Thompson[12a] and Rychnovsky[12b] on the cyclization of (*Z*)-homoallylic acetals and α-acetoxy ethers.

Since many natural products incorporating substituted tetrahydropyrans possess an alcohol at C-4, we concentrated the remainder of this study on the synthesis of 4-hydroxy-2,3,6-trisubstituted tetrahydropyrans starting from homoallylic alcohol **10** (Scheme 4). Alkyne **9** was prepared by

Scheme 4. Cyclization of **10**[a]



[a] Conditions: (a) Na, NH_3, ^{t}BuOH, −30 °C (94%); (b) EtCHO, TFA, CH_2Cl_2 (97%).

coupling 1-methoxybut-3-yne with propylene oxide. Reduction of **9** using sodium in liquid ammonia in the presence of *tert*-butyl alcohol gave homoallylic alcohol **10** in 94% yield (Scheme 4). The ratio of (*E*):(*Z*)-alkenes was approximately 9:1 as determined by NMR spectroscopy. Reaction of **10** with propanal in the presence of TFA gave tetrahydropyrans **11** and **12** in 97% yield and as a 93:7 mixture of epimers at

(8) 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.

(9) Ley and co-workers have demonstrated that reaction of homoallylic tetrahydropyranyl ethers with TFA gave mono- and bicyclic alkenols in good yields: (a) Buffet, M. F.; Dixon, D. J.; Edwards, G. L.; Ley, S. V.; Tate, E. W. *J. Chem. Soc., Perkin Trans. 1* **2000**, 1815. (b) Dixon, D. J.; Ley, S. V.; Tate, E. W. *J. Chem. Soc., Perkin Trans. 1* **2000**, 1829.

(10) Hoffmann and co-workers have used $SnCl_4$ to prepare a dihydropyran from a THP-protected hydroxy-vinylsilane: Hoffmann, R. W.; Giesen, V.; Fuest, M. *Liebigs Ann. Chem.* **1993**, 629.

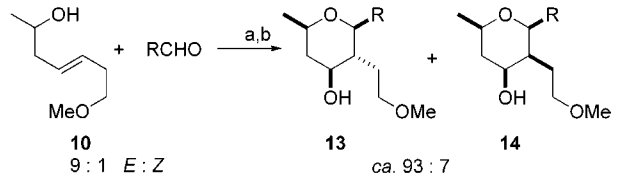
(11) An alternative approach to introduce a range of substituents into C-2 is via the segment-coupling Prins cyclization as described by Rychnovsky, S. D.; Marumoto, S.; Jaber, J. J.; Vitale, J. P.; Rychnovsky, S. D. *Org. Lett.* **2002**, *4*, 3919 and refs cited therein.

(12) Examples of cyclizations of *cis*-olefins include: (a) Winstead, R. C.; Simpson, T. H.; Loch, G. A.; Schiavelli, M. D.; Thompson, D. W. *J. Org. Chem.* **1986**, *51*, 275. (b) Jaber, J. J.; Mitsui, K.; Rychnovsky, S. D. *J. Org. Chem.* **2001**, *66*, 4679.

C-3 in favor of the all-equatorial diastereomer (as determined by ^{1}H and ^{13}C NMR spectroscopy). This result is in accord with the stereochemical outcome of the cyclizations illustrated in Scheme 3 when the ratio of (*E*):(*Z*)-alkenes in the starting material **10** is taken into account.

To investigate the generality of this cyclization process, homoallylic alcohol **10** was reacted with a range of aldehydes (Table 1).

Table 1. Reaction of Homoallylic Alcohol **10** with a Range of Aldehydes[a]



10 9 : 1 *E* : *Z* **13** + **14** *ca.* 93 : 7

(a) TFA, CH_2Cl_2; (b) K_2CO_3, MeOH

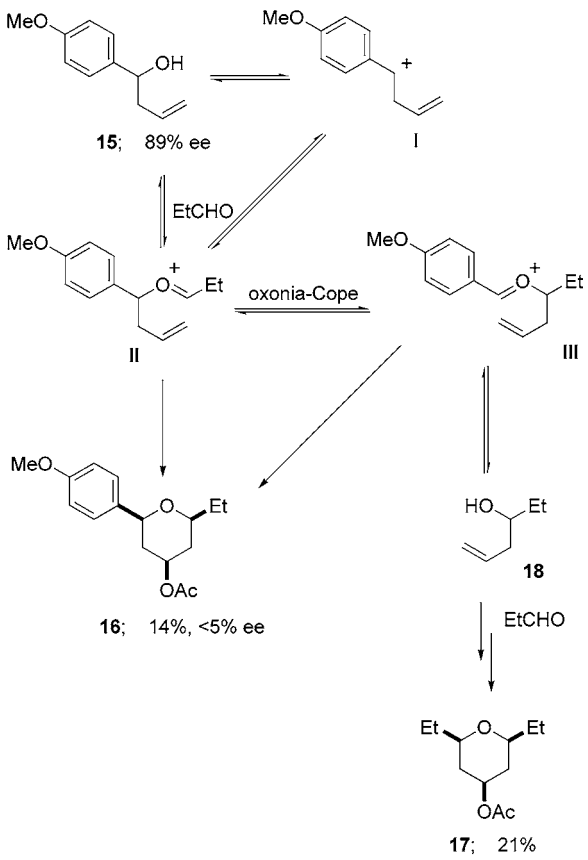
entry		R	yields **13** + **14** (%)
i	**13a**	$H_2C{=}CHCH_2CH_2$	97
ii	**13b**	$CH_3CH{=}CH$	47
iii	**13c**	$H_2C{=}CH$	65
iv	**13d**	Ph	63
v	**13e**	2-BrC_6H_4	65
vi	**13f**	4-$(OMe)C_6H_4$	39[b]
vii	**13g**	$PhCH_2CH_2$	84
viii	**13h**		73

[a] Conditions: (a) Na, NH_3, ^{t}BuOH, −30 °C (94%); (b) EtCHO, TFA, DCM (97%) [b] Starting material (39%) was recovered.

In each case, the resultant trifluoroacetate was hydrolyzed with potassium carbonate in methanol to give the 4-hydroxy-2,3,6-trisubstituted tetrahydropyran. The products were obtained in good yields, but the reactions were less efficient when α,*β*-unsaturated or benzylic aldehydes were used compared with aldehydes with a saturated center α to the carbonyl (i.e., entries i and vii).

If these reactions are to be used to good effect in natural product synthesis, clearly they need to be readily adapted for the enantioselective synthesis of tetrahydropyrans. Recently, we have shown that, in the case of a benzylic homoallylic alcohol possessing an electron-donating group, e.g., **15** (89% ee), that loss of stereochemical integrity was observed during the cyclization to give **16** (<5% ee), a process that is believed to be occurring via a stabilized benzylic cation intermediate **I** (Scheme 5).[13] To ensure than no racemization is occurring during the cyclizations to the tetrasubstituted tetrahydropyrans, (*S*)-homoallylic alcohol (*S*)-**10** was prepared from (*S*)-propylene oxide in 99% ee (as determined from the Mosher's ester derivatives) and as ca. 9:1 mixture of (*E*):(*Z*)-isomers (Scheme 6). Treatment of (*S*)-**10** with 3-phenylpropanal and TFA gave, after hydrolysis

Scheme 5 [a]

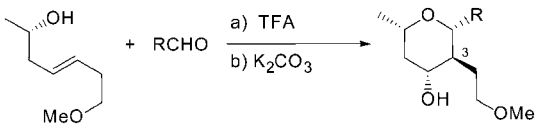


[a] Conditions: $BF_3{\cdot}Et_2O$, AcOH, TMSOAc.

of the esters with potassium carbonate, the diastereomeric alcohols **13g** and **14g** in approximately a 93:7 ratio and 81% overall yield. The products were separated by HPLC and the major diastereomer **13g** analyzed by chiral HPLC confirming that it had retained the stereochemical integrity of the starting (*S*)-homoallylic alcohol (*S*)-**10** of >99% ee.

In this case, using homoallylic alcohol **10** (in which the side-chain is not aromatic) would not favor formation of the stabilized carbocation **I**. When propanal and a benzylic alcohol with an electron-donating substituent, e.g., **15**, is used in the Prins cyclization, the symmetrical tetrahydropyran **17** predominates (Scheme 5). We proposed that **17** is formed via a side-chain exchange process initiated by an oxonia−Cope rearrangement (**II** to **III**).[13] The outcome of the reaction will be dependent upon the equilibria for the sequence **I** to

Scheme 6. Cyclization of Enantioenriched Homoallylic Alcohols



(*S*)-**10** >99% ee

R= $PhCH_2CH_2$ **(-)-13f** >99% ee

R= 4-$(OMe)C_6H_4$ **(-)-13g** >99% ee

(13) (a) Crosby, S. R.; Harding, J. R.; King, C. D.; Parker, G. D.; Willis, C. L. *Org. Lett.* **2002**, *4*, 577. (b) Crosby, S. R.; Harding, J. R.; King, C. D.; Parker, G. D.; Willis, C. L. *Org. Lett.* **2002**, *4*, 3407.

II to **III** to **18** (Scheme 5). For example, if 4-methoxybenzaldehyde were used in the cyclization reaction instead of propanal, the stereochemical integrity of an enantiopure starting material may be lost. To explore this, homoallylic alcohol (*S*)-**10** was treated with 4-methoxybenzaldehyde in the presence of TFA giving, after hydrolysis of the esters, a 93:7 mixture of the diastereomeric alcohols **13f** and **14f** (Scheme 6). The major product was shown to be essentially a single enantiomer from analysis of the Mosher's ester derivatives. In this case, TFA was used in the cyclization process, which contrasts with the reaction shown in Scheme 5, where $BF_3{\cdot}Et_2O$, AcOH, and TMSOAc (as a fluoride trap) were used.

Recently, Rychnovsky and co-workers[11] have shown that the extent of side-chain exchange processes and partial racemization in acid-promoted Prins cyclizations of benzylic homoallylic alcohols and aldehydes is dependent not only on the substituents on the aromatic ring but also on the reaction conditions employed. While reaction of a benzylic homoallylic alcohol with propanal and $BF_3{\cdot}Et_2O$, AcOH, and TMSOAc led to partial racemization, using $SnBr_4$, Rychnovsky and co-workers found that the reaction was more efficient and that the stereochemical integrity of the starting material was maintained in the resultant 4-bromotetrahydropyran.

Thus, in the final part of this investigation, we examined the reaction of homoallylic alcohol (*S*)-**10** and 4-methoxybenzaldehyde with $BF_3{\cdot}Et_2O$, TMSOAc, and AcOH and obtained the product **13f** in 66% yield and >99% ee, similar to the results obtained using TFA followed by hydrolysis of the resultant trifluoroacetate (Scheme 6). In this case, the reaction conditions (i.e., TFA or $BF_3{\cdot}Et_2O$, TMSOAc, and AcOH) do not effect the overall outcome of the reaction and conversion of the oxycarbenium ion or oxonia−Cope rearrangement intermediates (analogous to **II** and **III**) to the tetrasubstituted tetrahydropyran is the preferred pathway.

In conclusion, a flexible and efficient approach to the synthesis of 4-hydroxy-2,3,6-tetrasubstituted tetrahydropyrans has been described involving the reaction of aldehydes, homoallylic alcohols, and TFA with the creation of three new stereocenters in a single-pot process. By changing the aldehyde component, a variety of functionalized side-chains can be installed at C-2. The method has been applied to the enantioselective synthesis of tetrahydropyrans **13f** and **13g** giving the products in good yields and >99% ee. This one-pot reaction has exciting potential for use in natural product synthesis. From the work described herein and from our previous studies,[13] it is apparent that care is needed in the retrosynthetic analysis of tetrahydropyrans with an aromatic side-chain at C-2 or C-6 (e.g., catechols from *Plectranthus sylvestris*[13b]). Ideally, the aromatic portion of the target molecule should be derived from the requisite substituted benzylic aldehyde, not from a benzylic homoallylic alcohol. An alternative approach to the synthesis of such molecules is the use of segment-coupling Prins cyclization.[11]

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Supporting Information Available: Preparation and characterization of the compounds described in the paper. This material is available free of charge via the Internet at http://pubs.acs.org.

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