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Stereoselective Synthesis of 2,6-*trans*-Tetrahydropyrans

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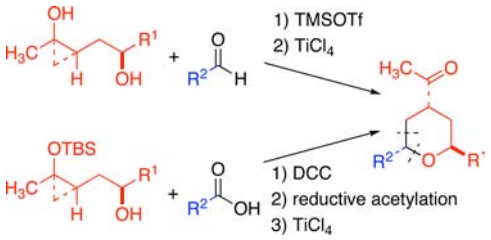
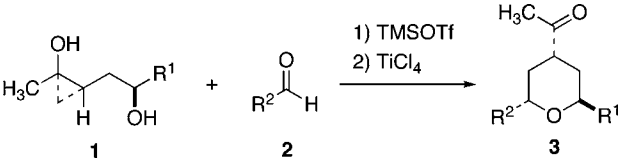
ABSTRACT



A stereoselective route to the thermodynamically unfavorable 2,6-*trans*-tetrahydropyrans has been developed from coupling of hydroxyethyl-tethered cyclopropanols and aliphatic aldehydes. Noteworthy is high convergency from direct coupling of two segments.

Functionalized tetrahydropyran rings are frequently embedded in an array of bioactive natural products.[1] *cis*-2,6-Disubstituted tetrahydropyrans represent prevalent stereochemical motifs. Another important subunit features the corresponding 2,6-*trans* stereochemistry. Enantio- and stereoselective syntheses of these tetrahydropyrans have been an active area of research. There are a large number of efficient methods for preparing thermodynamically favorable 2,6-*cis*-tetrahydropyrans.[2] In contrast, only a handful of general methods are available for preparing the more challenging 2,6-*trans*-tetrahydropyrans by direct coupling of two segments.[3−6] Building on our synthesis of all-*cis*-2,4,6-trisubstituted tetrahydropyrans by the use of a cyclopropanol as a homoenol,[7,8] we report herein a new method for the stereoselective preparation of the corresponding 2,6-*trans*-tetrahydropyrans (THPs) (Scheme 1).

Scheme 1



Treatment of cyclopropanol **4** and aldehyde **2** with TMSOTf (excess) was previously shown to afford easy access to all-*cis*-2,4,6-trisubstituted THPs **5** (Scheme 2).[7a] This simple method takes advantage of the titanium-mediated cyclopropanation of homoallylic alcohols[9] and

(1) For reviews, see: (a) Norcross, R. D.; Paterson, I. *Chem. Rev.* **1995**, *95*, 2041. (b) Mulzer, J.; Öhler, E. *Chem. Rev.* **2003**, *103*, 3753. (c) Kang, E. J.; Lee, E. *Chem. Rev.* **2005**, *105*, 4348. (d) Morris, J. C.; Nicholas, G. M.; Phillips, A. J. *Nat. Prod. Rep.* **2007**, *24*, 87.

(2) For reviews, see: (a) Boivin, T. L. B. *Tetrahedron* **1987**, *43*, 3309. (b) Clarke, P. A.; Santos, S. *Eur. J. Org. Chem.* **2006**, 2045. (c) Larrosa, I.; Romea, P.; Urpí, F. *Tetrahedron* **2008**, *64*, 2683.

(3) Lewis, M. D.; Cha, J. K.; Kishi, Y. *J. Am. Chem. Soc.* **1982**, *104*, 4976.

(4) (a) Huang, H.; Panek, J. S. *J. Am. Chem. Soc.* **2000**, *122*, 9836. (b) Lowe, J. T.; Panek, J. S. *Org. Lett.* **2005**, *7*, 3231. (c) Markó, I. E.; Dobbs, A. P.; Scheirmann, V.; Chellé, F.; Bayston, D. J. *Tetrahedron Lett.* **1997**, *38*, 2899.

(5) (a) Trost, B. M.; Machacek, M. R.; Faulk, B. D. *J. Am. Chem. Soc.* **2006**, *128*, 6745. (b) Trost, B. M; Machacek, M. R. *Angew. Chem., Int. Ed.* **2002**, *41*, 4693. (c) Hansen, E. C.; Lee, D. *Tetrahedron Lett.* **2004**, *45*, 7151.

(6) See also: (a) Ireland, R. E.; Thaisrivongs, S.; Vanier, N.; Wilcox, C. S. *J. Org. Chem.* **1980**, *45*, 48. (b) Semmelhack, M. F.; Bodurow, C. *J. Am. Chem. Soc.* **1984**, *106*, 1496. (c) Danishefsky, S. J.; DeNinno, S.; Lartey, P. *J. Am. Chem. Soc.* **1987**, *109*, 2082. (d) McDonald, F. E.; Singhi, A. D. *Tetrahedron Lett.* **1997**, *38*, 7683.

(7) (a) Lee, H. G.; Lysenko, I.; Cha, J. K. *Angew. Chem., Int. Ed.* **2007**, *46*, 3326. See also: (b) Epstein, O. L.; Lee, S.; Cha, J. K. *Angew. Chem., Int. Ed.* **2006**, *45*, 4988.

(8) See also: O'Neil, K. E.; Kingree, S. V.; Minbiole, K. P. C. *Org. Lett.* **2005**, *7*, 515.

(9) Quan, L. G.; Kim, S.-H.; Lee, J. C.; Cha, J. K. *Angew. Chem., Int. Ed.* **2002**, *41*, 2160.

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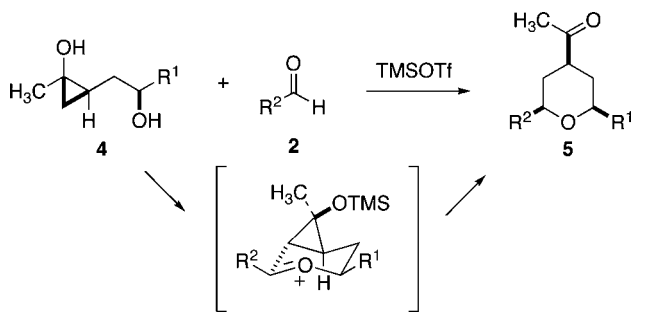
Scheme 2



is applicable to a full range of aldehydes. The observed stereochemical outcome is in accord with a chairlike transition state.

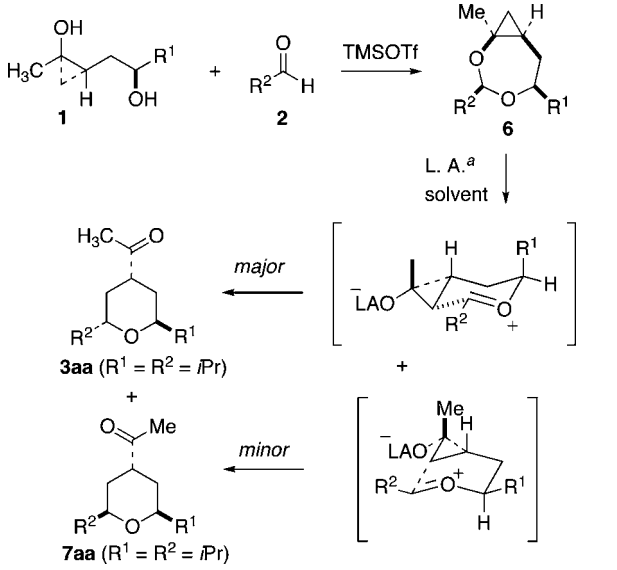
We were intrigued by the corresponding annulation of cyclopropanol **1**, which is epimeric to **4**, to access 2,6-*trans* THPs; a priori, formation of two epimers, having opposite configuration at the newly created stereocenter, was possible. Seven-membered cyclic acetal **6** was obtained as a single isomer in nearly quantitative yield on treatment of **1a** (R^1 = *i*-Pr) and *i*-butyraldehyde (**2a**: R^2 = *i*-Pr) with TMSOTf by Noyori's or Kurihara's procedures.[10] In contrast to facile formation of **5** from **4**, however, treatment of **6** with TMSOTf gave complex reaction mixtures with little THP formation.[11] The use of $TiCl_4$ was necessary to deliver a 14:1 mixture of **3aa** and **7aa** in 80−82% yield (Table 1).[12] Among several Lewis acids screened, $BF_3\cdot Et_2O$ and $HBF_4\cdot OEt_2$ furnished **3aa** in lower yields. Other Lewis acids were ineffective, in which poor yield (with $SnCl_4$), hydrolysis of of **6** (to give starting diol **1a**; with $Ti(OiPr)Cl_3$ or TfOH), or an unidentified complex mixture (with $EtAlCl_2$) was obtained. The use of nitroethane as solvent resulted in a modest improvement in diastereoselectivity.[13]

The stereochemistry of **3aa**−**3ad**[13] was unequivocally established on the basis of key coupling constants and is suggestive of the preponderance of a chairlike transition state. Electrophilic ring-opening of cyclopropanes by oxocarbenium ions is believed to proceed via "corner attack"[14] at the less substituted C−C bond, and the corner-opening pathway could be accommodated by slightly tweaking the cyclopropanol moiety toward the *E*-oxocarbenium ion.

We examined functional group compatibility with several aldehydes under typical conditions employing $TiCl_4$ with or without 0.2 equiv of 2,6-di-*t*-butyl-4-methylpyridine in CH_2Cl_2. A β-alkoxy substituent in the aldehyde partner (e.g., **9** and **12**) was tolerated, but THP formation was sluggish in the case of **10**, bearing a γ-siloxy substituent (Scheme 3).

A series of competition experiments were next performed to compare the nucleophilicity of cyclopropanol

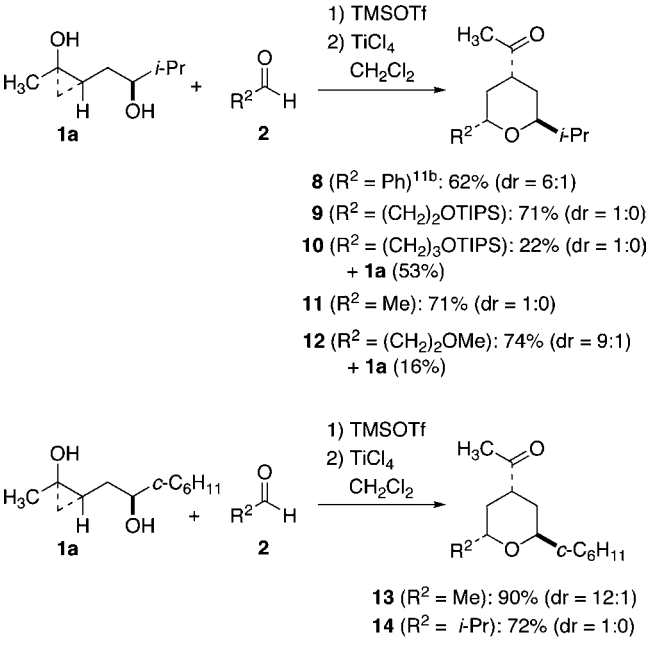
Table 1. Preparation of 2,6-*trans*-Tetrahydropyran **3aa**



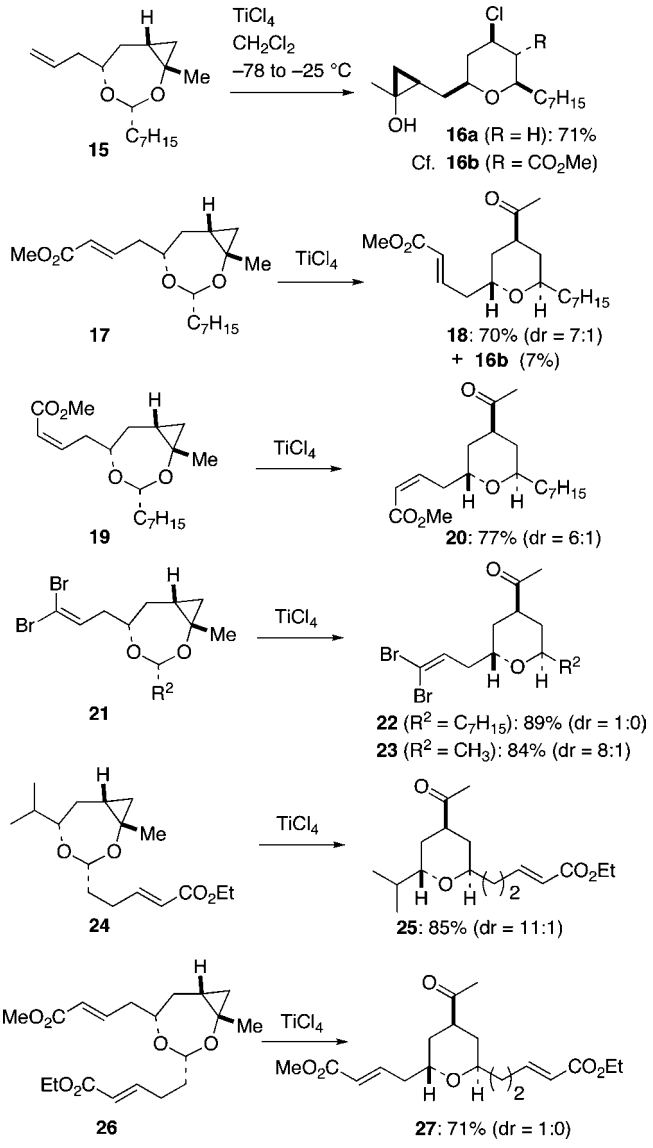
entry	acid[a]	additive	solvent	temp (°C)	yield (%) (dr)
1	$TiCl_4$	–	CH_2Cl_2	−78 to −25	80 (14:1)
2	$TiCl_4$	base[c]	CH_2Cl_2	−78 to −25	95 (11:1)
3	$TiCl_4$	Na_2SO_4	CH_2Cl_2	−78 to −25	92 (17:1)
4	$TiCl_4$	4 Å MS	CH_2Cl_2	−78 to −25	93 (12:1)
5	$TiCl_4$	Na_2SO_4	[d]	−55	90 (14:1)
6	$BF_3\cdot Et_2O$	–	CH_2Cl_2	−78 to −25	33 (3:1)[e]
7	$HBF_4\cdot OEt_2$[b]	–	CH_2Cl_2	−40 to 0	42 (6:1)
8	$HBF_4\cdot OEt_2$	–	CH_2Cl_2	0	63 (5:1)
9	$HBF_4\cdot OEt_2$	–	CH_2Cl_2	−40	54 (11:1)
10	$HBF_4\cdot OEt_2$	–	CH_3CN	−20	66 (3:1)[f]

[a] Except in entry 7, 1.0 equiv was used. [b] $HBF_4\cdot OEt_2$ (0.2 equiv) was used. [c] 2,6-di-*t*Butyl-4-methylpyridine (0.2 equiv) was used. [d] 1:1 $CH_2Cl_2/CF_3C_6H_5$ was used as solvent. [e] Diol **1a** was also isolated in 25% yield. [f] Diol **1a** was also isolated in 30% yield.

Scheme 3

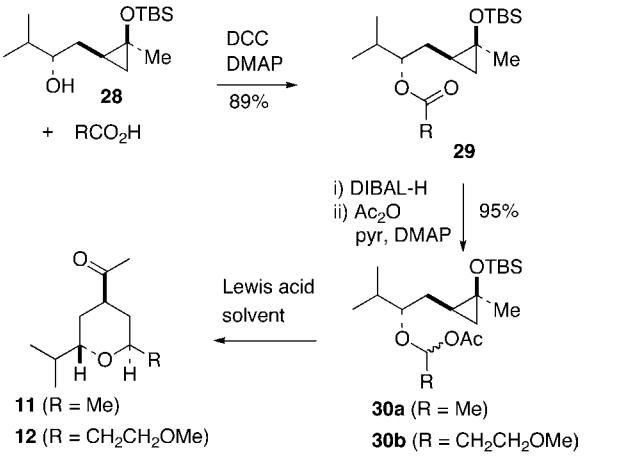


Scheme 4



with the Prins cyclization of the pendant olefin (Scheme 4). The requisite substrates were prepared from readily available racemic or enantiopure cyclopropanols by inversion

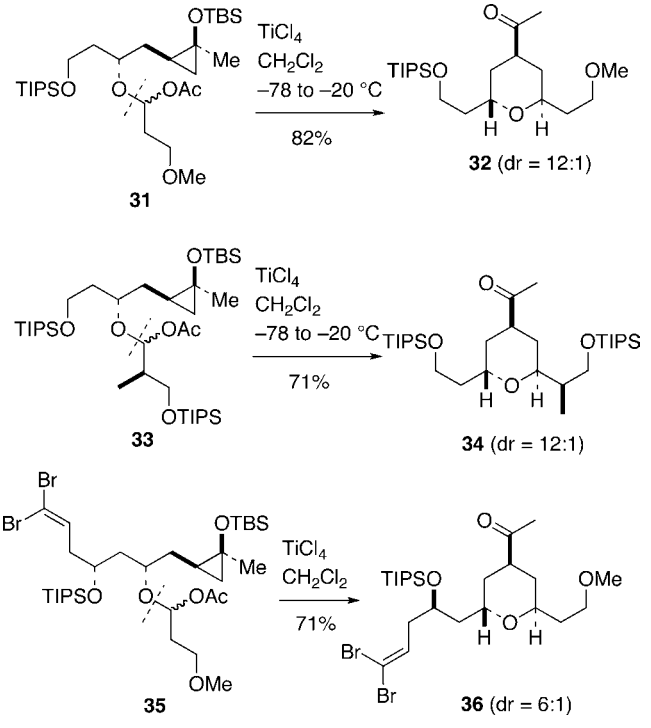
Table 2. THP Synthesis via Reductive Acetylation



entry	30a,b	acid[a]	additive	solvent	temp (°C)	yield (%) (dr)
1	**30a**	$TiCl_4$	–	CH_2Cl_2	−78 to −25	72 (1:0)
2	**30a**	$MgBr_2 \cdot OEt_2$[b]	4 Å MS	CH_2Cl_2	−78 to rt	62 (10:1)
3	**30a**	$BF_3 \cdot Et_2O$	4 Å MS	CH_2Cl_2	−78 to −25	42 (1:0)
4	**30a**	$BF_3 \cdot Et_2O$[b]	4 Å MS	CH_3CN	−40 to −20	54 (11:1)
5	**30b**	$TiCl_4$	–	CH_2Cl_2	−78 to −25	78 (9:1)
6	**30b**	$TiCl_4$	base[c]	CH_2Cl_2	−78 to −25	81 (9:1)
7	**30b**	$MgBr_2 \cdot OEt_2$[b]	4 Å MS	CH_2Cl_2	−50 to rt	34 (7:1)
8	**30b**	$BF_2 \cdot Et_2O$	4 Å MS	CH_3CN	−40 to rt	55 (9:1)

[a] Unless indicated otherwise, 1.1 equiv was used. [b] 3.0 equiv was used. [c] 2,6-di-*t*Butyl-4-methylpyridine (0.2 equiv) was used.

Scheme 5



of the tethered secondary alcohols or asymmetric allylation of the corresponding aldehydes.[9,15] In the case of **15**,

(10) (a) Murata, S.; Suzuki, M.; Noyori, R. *Tetrahedron* **1988**, *44*, 4259. (b) Kurihara, M.; Hakamata, W. *J. Org. Chem.* **2003**, *68*, 3413.

(11) (a) Interestingly, treatment of conjugated aldehydes (α,β-unsaturated aldehyde, aromatic aldehyde, and alkynal) with TMSOTf yielded tetrahydrofurans as major products, along with small amounts of both THPs (e.g., **3** and **7**). Particularly noteworthy is atypical regiochemistry of the ring-opening at the more substituted C−C bond of the cyclopropanol ring in the presence of a carbenium ion-stabilizing group. (b) In contrast to the reaction with TMSOTf, however, treatment of the seven-membered cyclic acetal derived from benzaldehyde and **1a** with $TiCl_4$ gave the corresponding THP in 62% yield in 6:1 selectivity.

(12) Acetal **6** was isolated for characterization but can also be used without further purification for subsequent THP formation by the action of $TiCl_4$.

(13) See the Supporting Information.

(14) Ring-opening of cyclopropanes is known to proceed via corner or edge attack. For related examples, see: Meyer, C.; Blanchard, N.; Defosseux, M.; Cossy, J. *Acc. Chem. Res.* **2003**, *36*, 766.

as expected, Prins cyclization (**15** → **16a**) of the terminal olefin was observed. The placement of an electron-withdrawing substituent on the double bond resulted in the preponderant formation of THPs (e.g., **18**, **20**, **22**, **23**, **25**, and **27**) having attractively functionalized side chains, which are suitable for subsequent elaboration.

We also investigated Rychnovsky's convergent method of utilizing α-acetoxy ethers as precursors to oxocarbenium ions for the THP synthesis to complement the aforementioned seven-membered cyclic acetal strategy.[16] This tactic began with esterification of alcohol **28**, followed by Rychnovsky's reductive acetylation of the resulting ester **29**, to furnish the corresponding α-acetoxy ether **30** in excellent yield (Table 2). Treatment with **30a** and **30b** with Lewis acid afforded THPs **11** and **12**, respectively. Among three Lewis acids, $TiCl_4$ was again found to be most effective. Higher diastereoselectivity was obtained at low reaction temperature.

(15) (a) Lee, H. G.; Lysenko, I. L.; Cha, J. K. *ARKIVOC* **2008**, *9*, 133. See also: (b) Lee, J.; Kang, C. H.; Kim, H.; Cha, J. K. *J. Am. Chem. Soc.* **1996**, *118*, 291.

(16) (a) Dahanukar, V. H.; Rychnovsky, S. D. *J. Org. Chem.* **1996**, *61*, 8317. (b) Sizemore, N.; Rychnovsky, S. D. *Org. Synth.* **2003**, *80*, 177.

Additional examples are shown in Scheme 5 and serve to illustrate the utility of this flexible approach.

In summary, a direct route to *trans*-2,6-disubstituted tetrahydropyrans has been devised by coupling of hydroxyethyl-tethered cyclopropanols with aliphatic aldehydes. This convergent method allows the union of two segments to rapidly build structural complexity by making use of cyclopropanols as homoenols. Studies are in progress to generate oxocarbenium ions for subsequent THP ring closure under milder conditions to be more fully compatible with basic functional groups.

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Supporting Information Available. Experimental details and spectroscopic data for key intermediates. This material is available free of charge via the Internet at http://pubs.acs.org

The authors declare no competing financial interest.