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Highly Stereoselective Prins Cyclization of (*Z*)- and (*E*)-γ-Brominated Homoallylic Alcohols to 2,4,5,6-Tetrasubstituted Tetrahydropyrans

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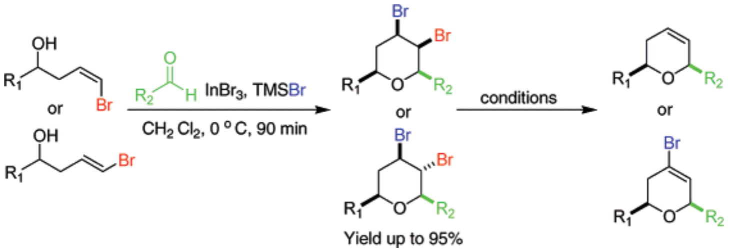
ABSTRACT



An efficient method has been developed to construct 2,6-*cis*-4,5-dibromo-tetrasubstituted tetrahydropyran (THP) rings with well-controlled stereochemistry in moderate to high yields.

Functionalized tetrahydropyran (THP) rings are key structural elements in many biologically active natural products, such as brevetoxin B, (−)-centrolobine, blepharocalyxin D and E, altromycin B, scytophycin C, and (−)-apicularen A.[1] Among the methods[2] available, Prins cyclization[3] offers one of the most versatile methods for the construction of substituted tetrahydropyrans. Our group recently developed a highly convergent approach to construct crossed 2,4,6-trisubstituted THP rings via Prins cyclization using indium-based mild Lewis acids,[4a] and its synthetic value was demonstrated in the successful total synthesis of (−)-centrolobine[4b] and the formal synthesis of (+)-SCH 351448.[4c] To further the development of this methodology, we felt that (*Z*)- and (*E*)-γ-brominated homoallylic alcohols[5,6] could be utilized to construct 2,6-*cis*-4,5-dihalo-tetrasubstituted THP rings in the presence of indium-based Lewis acids (Scheme 1).

We forsee that 2,4,5,6-tetrasubstituted THP rings are versatile intermediates that could allow further functionlization to form other THP-containing compounds. For instance, blepharocalyxins D and E are believed to be synthesized from a precursor with a selective double bond on the pyran ring from a biogenetic point of view.[1c] In the present letter, we report an efficient method to construct 2,6-*cis*-4,5-dibromo-

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[1] (a) Lin, Y.-Y.; Risk, M.; Ray, S. M.; Van Engen, D.; Clardy, J.; Golik, J.; James, J. C.; Nakanishi, K. *J. Am. Chem. Soc.* **1981**, *103*, 6773−6775. (b) De Albuquerque, I. L.; Galeffi, C.; Casinovi, C. G.; Marini-Bettolo, G. B. *Gazz. Chim. Ital.* **1964**, *94*, 287−295. (c) Ali, M. S.; Tezuka, Y.; Banskota, A. H.; Kadota, S. *J. Nat. Prod.* **2001**, *64*, 491−496. (d) Brill, G. M.; McAlpine, J. B.; Whittern, D. N.; Buko, A. M. *J. Antibiot.* **1990**, *43*, 229−237. (e) Ishibashi, M.; Moore, R. E.; Patterson, G. M. L.; Xu, C.; Clardy, J. *J. Org. Chem.* **1986**, *51*, 5300−5306. (f) Kunze, B.; Jansen, R.; Sasse, F.; Höfle, G.; Reichenbach, H. *J. Antibiot.* **1998**, *51*, 1075−1080.

[2] Radical cyclization see: (a) Lee, E.; Park, C. M.; Yun, J. S. *J. Am. Chem. Soc.* **1995**, *117*, 8017−8018. Hetero-Diels−Alder reaction see: (b) Liu, P.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2001**, *123*, 10772−10773. Hydroxy−epoxide cyclization see: (c) Nicolaou, K. C.; Prasad, C. V. C.; Somers, P. K.; Hwang, C. K. *J. Am. Chem. Soc.* **1989**, *111*, 5330−5334. Oxy-Michael reaction see: (d) Paterson, I.; Chen, D. Y.-K.; Coster, M. J.; Aceña, J. L.; Bach, J.; Gibson, K. R.; Keown, L. E.; Oballa, R. M.; Trieselmann, T.; Wallace, D. J.; Hodgson, A. P.; Norcross, R. D. *Angew. Chem., Int. Ed.* **2001**, *40*, 4055−4060. Claisen rearrangements see: (e) Ziegler, F. E. *Acc. Chem. Res.* **1977**, *10*, 227−232. Maitland−Japp reaction see: (f) Clarke, P. A.; Martin, W. H. C.; Hargreaves, J. M.; Wilson, C.; Blake, A. J. *Chem. Commun.* **2005**, *8*, 1061−1063.

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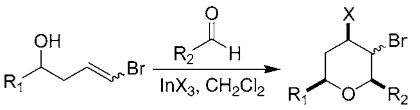
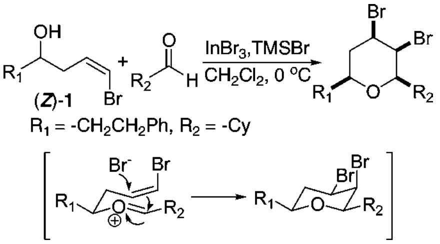
Scheme 1. Prins Cyclization of γ-Brominated Homoallylic Alcohol with Aldehydes



tetrasubstituted THP rings in moderate to high yields with excellent stereoselectivity and our explorations toward their synthetic value. To our best knowledge, our method is the first stereoselective dibromo-THP construction via Prins cyclization that results in a cis configuration of bromine atoms. Other approaches to dibromo-THP rings were realized via bromination of dihydropyrans, and only trans addition products were obtained.[7]

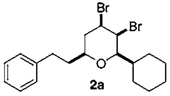
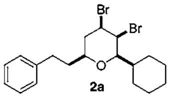
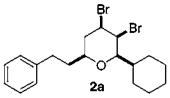
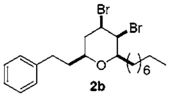
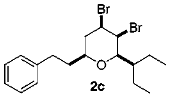
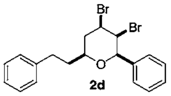
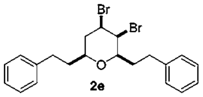
Scheme 2. Prins Cyclization of (*Z*)-**1** with Cyclohexanecarboxaldehyde and Analysis of the Stereochemistry



γ-Brominated homoallylic alcohol (*Z*)-**1** and cyclohexanecarboxaldehyde were selected for the optimization of reaction conditions (Scheme 2). Indium-based Lewis acids, such as InCl$_3$, In(OTf)$_3$, and InBr$_3$, were employed to mediate the Prins cyclization at 0 °C in CH$_2$Cl$_2$. No Prins product could be formed when InCl$_3$ was utilized to promote this cyclization and no desired crossed product could be obtained by using In(OTf)$_3$.

Gratifyingly, InBr$_3$ was discovered to be the highly efficient Lewis acid to promote this Prins cyclization and the yields were dependent on the amount of InBr$_3$ employed (Table 1, entries 1, 2, and 3), with the best condition being 1.0 equiv of InBr$_3$ with 1.2 equiv of TMSBr[8] in CH$_2$Cl$_2$ at 0 °C to afford **2a** in 95% yield as a single isomer (Table 1, entry 3). This cyclization proceeded smoothly with high stereoselectivity and introduced four stereogenic centers into the product in one step. 2,4,6-*cis*-5-*trans* THP ring **2a** was expected to be constructed with an axial bromine substituent at the 5 position and the other three substituents occupying equatorial positions. This was confirmed by the crystal structure of **2a**[9] (Figure 1). We thus predict that *all-cis*-

Table 1. Prins Cyclization of (*Z*)-**1** with Aldehydes

entry	R$_2$	product	yield (%)[a]
1	-Cy	 **2a**	32[b]
2	-Cy	 **2a**	63[c]
3	-Cy	 **2a**	95
4	-(CH$_2$)$_7$CH$_3$	 **2b**	87
5	-CH(CH$_2$CH$_3$)$_2$	 **2c**	68
6	-Ph	 **2d**	71[d]
7	-CH$_2$CH$_2$Ph	 **2e**	91

[a] Isolated yield. [b] 0.2 equiv of InBr$_3$ was employed. [c] 0.5 equiv of InBr$_3$ was employed. [d] Reaction time was 25 h.

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(3) (a) Arundale, E.; Mikeska, L. A. *Chem. Rev.* **1952**, *51*, 505−555. (b) Adams, D. R.; Bhatnagar, S. P. *Synthesis* **1977**, *10*, 661−672. (c) Coppi, L.; Ricci, A.; Taddei, M. *J. Org. Chem.* **1988**, *53*, 911−913. (d) Wei, Z. Y.; Li, S. J.; Wang, D.; Chan, T. H. *Tetrahedron Lett.* **1987**, *28*, 3441−3444. (e) Yang, J.; Viswanathan, G. S.; Li, C. J. *Tetrahedron Lett.* **1999**, *40*, 1627−1630. (f) Patterson, B.; Marumoto, S.; Rychnovsky, S. D. *Org. Lett.* **2003**, *5*, 3163−3166. (g) Wei, Z. Y.; Wang, D.; Li, S. J.; Chan, T. H. *J. Org. Chem.* **1989**, *54*, 5768−5774. (h) Coppi, L.; Ricci, A.; Taddei, M. *Tetrahedron Lett.* **1987**, *28*, 973−976. (i) Perron, F.; Albizati, K. F. *J. Org. Chem.* **1987**, *52*, 4128−4130. (j) Rychnovsky, S. D.; Hu, Y.; Ellsworth, B. *Tetrahedron Lett.* **1998**, *39*, 7271−7274. (k) Jasti, R.; Vitale, J.; Rychnovsky, S. D. *J. Am. Chem. Soc.* **2004**, *126*, 9904−9905. (l) Carreño, M. C.; Des Mazery, R.; Urbano, A.; Colobert, F.; Solladié, G. *J. Org. Chem.* **2003**, *68*, 7779−7787. (m) Semeyn, C.; Blaauw, R. H.; Hiemstra, H.; Speckamp, W. N. *J. Org. Chem.* **1997**, *62*, 3426−3427. (n) Dalgard, J. E.; Rychnovsky, S. D. *J. Am. Chem. Soc.* **2004**, *126*, 15662−15663. (o) Huang, H.; Panek, J. S. *J. Am. Chem. Soc.* **2000**, *122*, 9836−9837.

(4) (a) Chan, K. P.; Loh, T. P. *Tetrahedron Lett.* **2004**, *45*, 8387−8390. (b) Chan, K. P.; Loh, T. P. *Org. Lett.* **2005**, *7*, 4491−4494. (c) Chan, K. P.; Ling, Y. H.; Loh, T. P. *Chem. Commun.* **2007**, *9*, 939−941.

(5) (a) Mallaiah, K.; Satyanarayana, J.; Ila, H.; Junjappa, H. *Tetrahedron Lett.* **1993**, *34*, 3145−3148. (b) Hoffmann, R. W.; Landmann, B. *Tetrahedron Lett.* **1983**, *24*, 3209−3212. (c) Lin, M. J.; Loh, T. P. *J. Am. Chem. Soc.* **2003**, *125*, 13042−13043. (d) Markó, I. E.; Dobbs, A. P.; Scheirmann, V.; Chellé, F.; Bayston, D. J. *Tetrahedron Lett.* **1997**, *38*, 2899−2902. (e) Björkling, F.; Norin, T.; Unelius, C. R.; Miller, R. B. *J. Org. Chem.* **1987**, *52*, 292−294. (f) Miller, R. B.; McGarvey, G. *J. Org. Chem.* **1978**, *43*, 4424−4431.

(6) (*Z*)-**1** was prepared in 62% yield by using hydrocinnamaldehyde to trap allylic anion generated from allyl bromide in the presence of LDA and zinc bromide.[5a] (*E*)-**1** was prepared in three steps: (1) propargylation of trialkylsilyl propargyl bromide with hydrocinnamaldehyde mediated with indium and indium bromide (60%),[5c] (2) DIBAL-H reduction converting the triple bond into the cis double bond (64%),[5d] and (3) bromination (90%).[5e,f]

(7) (a) Woods, G. F.; Temin, S. C. *J. Am. Chem. Soc.* **1950**, *72*, 139−143. (b) Dale, W. J.; Sisti, A. J. *J. Am. Chem. Soc.* **1954**, *76*, 81−82. (c) Brown, R. K.; Srivastava, R. M.; Sweet, F.; Murry, T. P. *J. Org. Chem.* **1971**, *36*, 3633−3636. (d) Brown, R. K.; Srivastava, R. M.; Sweet, F. *J. Org. Chem.* **1972**, *37*, 190−195.

(8) Our initial investigations revealed that TMSBr serves as a bromide source. No reaction occurred when only TMSBr was used as promoter. With a stoichiometric amount of InBr$_3$ as the sole promoter, only a trace amount of the product could be observed when (*Z*)-**1** was reacted with cyclohexanecarboxaldehyde; for (*E*)-**1** only 21% yield was obtained.

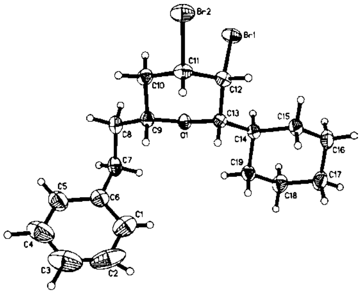
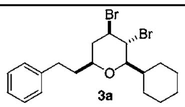
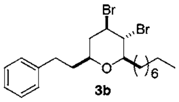
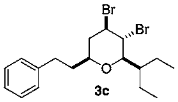
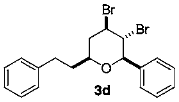
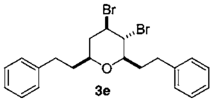


Figure 1. Crystal structure of **2a**, showing an axial bromine at the 5 position and all equatorial substituents at the 2,4,6 positions.

2,4,5,6-tetrasubstituted THP products would be formed when (*E*)-**1** was utilized.

By using the above optimized reaction condition[10] (Table 1, entry 3), a variety of aldehydes were selected to construct the 2,6-*cis*-4,5-dibromo-THP rings with both (*Z*)-**1** and (*E*)-**1** and moderate to good yields with excellent stereoselectivities were obtained. The results are summarized in Tables 1 and 2.

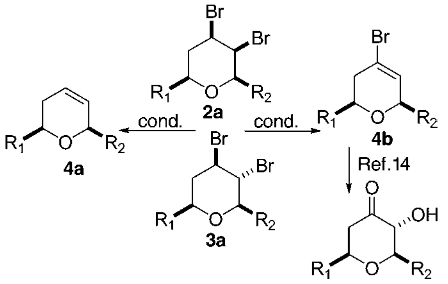
Table 2. Prins Cyclization of (*E*)-**1** with Aldehydes

entry	R_2	product	yield (%)[a,b]
1	-Cy	 **3a**	92
2	-$(CH_2)_7CH_3$	 **3b**	82
3	-$CH(CH_2CH_3)_2$	 **3c**	90
4	-Ph	 **3d**	77
5	-CH_2CH_2Ph	 **3e**	90

[a] Isolated yield. [b] Reaction time was 1.5 h.

THP products **2a** and **3a** were selected to perform a series of chemical transformations to explore synthetic versatilities of such dibromo-THP rings (Scheme 3). As expected, **4a** was readily obtained with a selective double bond via direct debromination by using activated zinc in acetic acid at room temperature,[11] and an unexpected alternative approach was also discovered to create such a selective double bond under radical reaction conditions (Table 3, entries 3 and 4).

Scheme 3. Chemical Transformations of 2,6-*cis*-4,5-Dibromo-THP Rings



The presence of an axial bromine makes **2a** more reactive with respect to **3a** (all bromines equatorial). The double bond of **4a** allows further functionalizations, such as epoxidation[12] and hydroxylation.[13] In addition, elimination product **4b** was formed when **2a** and **3a** were treated with potassium *tert*-butoxide. **2a** was again found to be more reactive than **3a**. Results are summarized in Table 3. Vinyl bromide **4b** is also a versatile intermediate that can be converted into 2,6-alkyl-3-hydroxytetrahydropyran-4-one via osmium-catalyzed cis dihydroxlation or into the 2,6-disubstituted THP ring upon catalytic hydrogenation with Pd/C.[14]

Table 3. Chemical Transformations of 2,6-*cis*-4,5-Dibromo-THP Rings

entry	substrate	conditions	product	yield (%)[a]
1	**2a**	Zn, AcOH, rt, 24 h	**4a**	70
2	**3a**	Zn, AcOH, rt, 24 h	**4a**	58
3	**2a**	Bu_3SnH, ABCCN, $PhCH_3$, reflux, 24 h	**4a**	71
4	**3a**	Bu_3SnH, ABCCN, $PhCH_3$, reflux, 24 h	**4a**	56
5	**2a**	*t*-BuOK, EtOH, rt, 24 h	**4b**	69
6	**3a**	*t*-BuOK, $PhCH_3$, reflux, 24 h	**4b**	59

[a] Isolated yield.

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[9] For crystal data for **2a** see the Supporting Information.

[10] **Typical experimental procedures for our Prins cyclization to 2,6-*cis*-4,5-dibromo-THP rings**: to an oven-dried round-bottomed flask with a magnetic stirrer was added indium bromide (106.0 mg, 0.30 mmol, 1.0 equiv) and anhydrous dichloromethane (1.5 mL). The mixture was vigorously stired at 0 °C. (*Z*)-**1** (91.8 mg, 0.36 mmol, 1.2 equiv) dissolved in 1 mL of anhydrous CH_2Cl_2 was introduced into the suspension, and 5 min later bromotrimethylsilane (TMSBr, 0.05 mL, 0.36 mmol, 1.2 equiv) was added. Cyclohexanecarboxaldehyde (33.7 mg, 0.30 mmol, 1.0 equiv) dissolved in 1 mL of anhydrous CH_2Cl_2 was slowly introduced over 10 min. The reaction was allowed to proceed at 0 °C for 90 min before being quenched with saturated sodium bicarbonate solution (5 mL). The aqueous layer was extracted with diethyl ether (3 × 10 mL) and the combined organic extracts were washed with brine, dried over anhydrous magnesium sulfate, filtered, and concentrated in vacuo. The residual crude product was purified via flash chromatography (0.5% diethyl ether in hexane) to afford **2a** as a white solid in 95% yield.

[11] Sato, F.; Akiyama, T.; Iida, K.; Sato, M. *Synthesis* **1982**, *12*, 1025−1026.

[12] Schmidt, B.; Wildemann, H. *Eur. J. Org. Chem.* **2000**, *18*, 3145−3163.

[13] Dobbs, A. P.; Guesné, S. J. J.; Martinović, S.; Coles, S. J.; Hursthouse, M. B. *J. Org. Chem.* **2003**, *68*, 7880−7883.

In conclusion, we have developed an efficient Prins cyclization reaction to construct 2,6-*cis*-4,5-dibromo-tetrasubstituted THP rings with high stereoselectivity in good yields. Effective manipulation of the stereochemistry of the bromine substituent at the 5 position was achieved by controlling the geometric configuration of the γ-brominated homoallylic alcohols. Our dibromo-THP products serve to provide versatile intermediates that allow further functionalization to various substituted pyran-containing compounds. Efforts are ongoing in applying this developed methodology to the synthesis of highly funtionalized tetrahydropyrans.

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

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(14) Miranda, P. O.; Díaz, D. D.; Pardón, J. I.; Bermejo, J.; Martín, V. S. *Org. Lett.* **2003**, *5*, 1979−1982.