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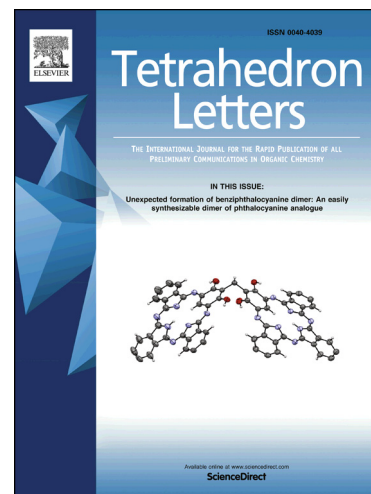
Synthesis of (S)-3-Hydroxytetrahydropyran from L-glutamic Acid

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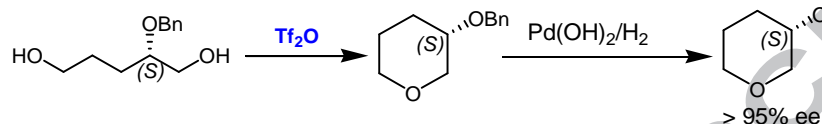
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Synthesis of (S)-3-Hydroxytetrahydropyran from L-glutamic Acid

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ABSTRACT

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A concise synthesis of (S)-3-hydroxytetrahydropyran from natural L-glutamic acid has been developed. The intramolecular etherification starting from 1, 5-diol was promoted by trifluoromethanesulfonic anhydride. The clinnamates of the alcohols were prepared for accurately determining the optical purity by HPLC method.

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Keywords:

(S)-3-hydroxytetrahydropyran

Trifluoromethanesulfonic anhydride

Intramolecular etherification

Introduction

As major components of the chiral drugs, the chiral organic molecules play an increasingly important role in pharmaceutical. The enantiomers of a chiral drug have shown different pharmacokinetic, pharmacodynamics and toxicological properties in human body.¹ The demand for chiral compounds is dramatically increasing accompany with the rapid growth of pharmaceutical research and development. This has brought prosperity in asymmetric synthesis² and resolution methodology.³ Preparing target chiral compounds from natural chiral materials, affords a facile and economic solution for chiral synthesis.

3-Hydroxytetrahydropyran forms an important substructure of some pharmacologically active compounds. These compounds seem to confer certain valuable properties on potential drugs. For examples, 3-hydroxytetrahydropyran containing compounds (**Figure 1**) are potential Soft ROCK inhibitor (**A**),⁴ glucokinase activator (**B**),⁵ Mnk2 kinases inhibitors (**C** and **D**),⁶ respectively.

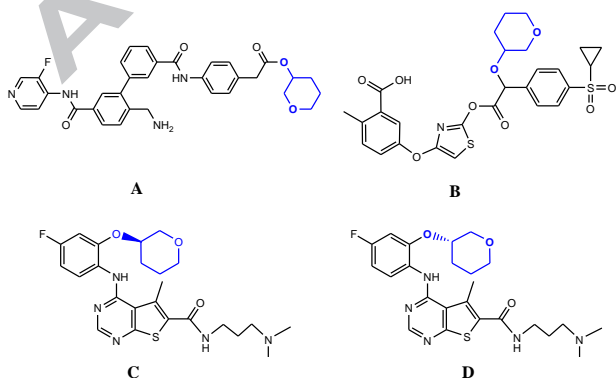


Figure 1. 3-Hydroxytetrahydropyran containing drugs

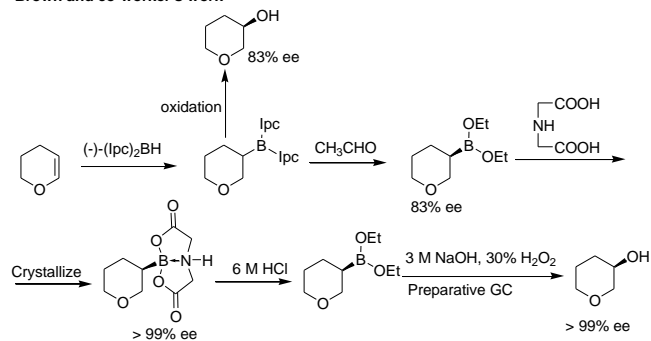
The racemic 3-hydroxytetrahydropyran was firstly synthesized in the year of 1959 by Barker and co-workers.⁷ To date, various methods for the synthesis of racemic 3-hydroxytetrahydropyran

have been developed.⁸ Hydroboration-oxidation of 3, 4-dihydro-2H-pyran can afford dozens of grams of 3-hydroxytetrahydropyran.⁹ However, the enantiomers of 3-hydroxytetrahydropyran with high optical purity are not easily synthesized. So far, utilizing the asymmetric hydroboration-oxidation of 3, 4-dihydro-2H-pyran with optically pure organoboranes as reductive agent has been the major way for preparing chiral 3-hydroxytetrahydropyran.¹⁰ In the 1980s, Brown and co-workers^{10a-f} made outstanding works in the preparation of high enantiomeric purity diisopinocampheylborane, and using them in asymmetric hydroboration of cyclic olefin, ketones and so on. Among them, the method^{10a} for the synthesis of (R)-3-hydroxytetrahydropyran was described as follows (**Scheme 1**): Hydroboration-oxidation of 3, 4-dihydropyran with (-)-diisopinocampheylborane gave the (R)-3-hydroxytetrahydropyran in 83% ee.^{10b} Treatment of the 3-tetrahydropyran diisopinocampheylborane with acetaldehyde provides the diethyl boronate. Then, iminodiacetic acid converts this boronate into a crystalline chelate. After recrystallizations twice from DMSO, the optical purity was up to 99% ee. Then, the crystalline chelate was acidification, followed by oxidation to give the crude product. The alcohol was distilled and purified by preparative GC to afford the (R)-3-hydroxytetrahydropyran in > 99% ee. This method has some advantages for the synthesis of high optical purity 3-hydroxytetrahydropyran. However, the high optical purity diisopinocampheylborane was expensive and not stable to moisture. Besides Brown's method, Jacobsen and coworkers reported a synthesis of (S)-3-hydroxytetrahydropyran through a intramolecular kinetic resolution of epoxy alcohols catalyzed by a [CoIII(salen)] complex, and this method gave (S)-3-hydroxytetrahydropyran in 46% yield with 95% ee.¹¹

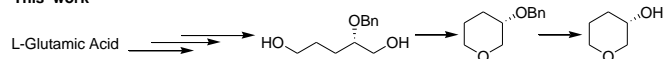
Using the chiral amino acids to prepare chiral pyran¹² and furan¹³ derivatives in kilograms scale have been reported with high optical purity. Herein, we report a protocol to prepare (S)-3-hydroxytetrahydropyran through intramolecular etherification of

1, 5-diol which can be transformed from available chiral starting material L-glutamic acid.

Brown and co-worker's work



This work



Scheme 1. Synthesis of 3-hydroxytetrahydropyran with high optical purity

Results and Discussion

In general, the process begins with the transformation of L-glutamic acid into a crucial intermediate (S)-2-(benzyloxy)pentane-1, 5-diol (**Table 1, compound 1**) which then undergoes cyclization and debenzoylation to isolate the product (S)-3-aminotetrahydrofuran.

At the outset of our studies, the (S)-2-(benzyloxy)pentane-1,5-diol was prepared from L-glutamic acid according to the literature.^{14, 15} The benzyl was chosen as the protecting group because of its stability under LiAlH_4 reduction condition and easy removal under mild conditions. To go insight of the crucial intramolecular etherification, some common closed loop methods were tried. When 1, 5-diol was treated with 0.2 eq. p-toluenesulfonic acid (entry 1), refluxed in toluene for 18 h with the water diversion device, no product was detected. Mitsunobu cyclization (entry 2) was tried and afforded the cyclization product **2** in the low yield of 15%. Intramolecular nucleophilic substitution reaction (entry 3) also used for the cyclization, but the yield was also unsatisfactory.

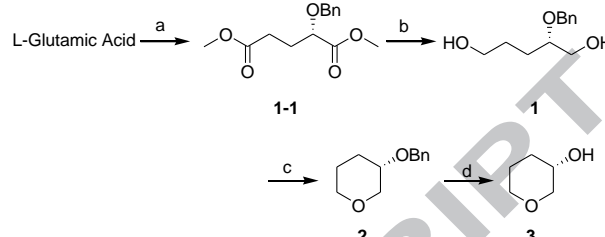
Table 1. Intramolecular etherification of 1, 5-diol.^{a, b, c}

entry	conditions	yield (%)
1	0.2 eq. TsOH, toluene, reflux, 18 h	n.d.
2	1.1 eq. DEAD, 1.1 eq. PPh_3 , THF, 20 h	15
3	1.0 eq. TsCl, 1.0 eq. NaH, THF, 0–25 °C, 4 h	10
4	1.0 eq. TFAA, 3.0 eq. Pyridine, DCM, 0–25 °C, 1 h	n.d.
5	1.0 eq. Ti_2O_3 , 3.0 eq. Pyridine, DCM, 0 °C, 1 h	n.d.
6	1.0 eq. Ti_2O_3 , 3.0 eq. Et_3N , DCM, 0–25 °C, 3 h	40
7	1.0 eq. Ti_2O_3 , 5% DMAP, 3.0 eq. Et_3N , DCM, 25 °C, 1 h	48

^aConditions: compound **1** (1 mmol). ^bThe isolated yield was obtained via silica gel column. ^cn.d. = not detected by GC–MS.

Trifluoroacetic anhydride (entry 4) and trifluoromethanesulfonic anhydride (entry 5) were designed as dehydration agents with excess of pyridine as base, but only the esterification reaction was detected. To our delight, when 1, 5-

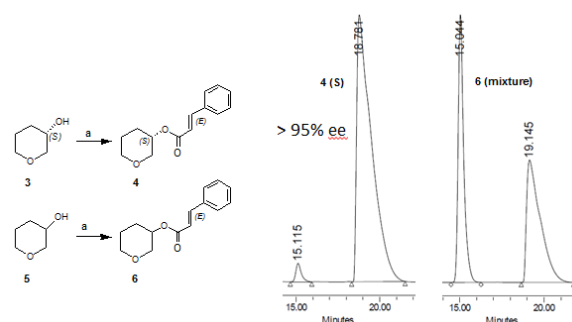
diol was treated with 1.0 eq. of trifluoromethanesulfonic anhydride, 3.0 eq. of triethylamine in dichloromethane at 0 °C to 25 °C for 3 h (entry 6), the compound **2** was isolated in 40% yield. Further investigation indicated that the addition of a catalytic amount of DMAP promoted the reaction and gave the compound **2** with 48% yield.



Reagents and conditions: (a) HCl (conc.), NaNO_2 , H_2O , -5 °C, 16 h; HCl (conc.), MeOH, reflux, 12 h; BnBr, Ag_2O , EtOAc, rt, 48 h; 65% yield (3 steps). (b) LiAlH_4 , Et_2O , 24 h, 85% yield; (c) Ti_2O_3 , DMAP, Et_3N , CH_2Cl_2 , 25 °C, 0.5 h, 49% yield; (d) $\text{Pd}(\text{OH})_2$, H_2 (1 atm), MeOH, 40 °C, 20 h, 82% yield.

Scheme. 2 Preparation of grams of (S)-3-hydroxytetrahydropyran.

Next, the grams scale of (S)-3-hydroxytetrahydropyran was prepared as shown in **Scheme 2**. Compound **1-1** was synthesized with yield of 65% in 3 steps from L-glutamic acid according to the literatures. Then compound **1-1** was treated with 2.0 eq. of LiAlH_4 in ether, and transformed into (S)-2-(benzyloxy)pentane-1, 5-diol in 85% yield.¹⁵ Treatment of 21.0 g of 1, 5-diol with the optimum conditions afforded the cyclization product **2** 9.4 g (49% yield). The benzyl protective group was removed using palladium hydroxide in MeOH at 40 °C under 1 atm H_2 to give the compound **3** with 85% yield. Determination of chiral purity of the product was achieved via chiral HPLC using the cinnamamide derivative¹¹ of the (S)-3-hydroxytetrahydropyran as illustrated in **Figure 2**. The results revealed that this method afforded the (S)-3-hydroxytetrahydropyran with high optical purity (> 95% ee) without other purification.



Reagents and Conditions: (a) Cinnamyl chloride, DMAP, Et_3N , DCM. (b) HPLC conditions: Daicel AD-H column (4.6×250 mm, 5 μm), mobile phase: *n*-heptane: i-PrOH = 0.9 : 0.03 (v/v); detector: UV, λ = 254 nm.

Figure 2. HPLC of cinnamamide derivatives.

Conclusion

In summary, (S)-3-hydroxytetrahydropyran with grams scale was prepared from inexpensive natural chiral L-glutamic acid. The intramolecular etherification was promoted by trifluoromethanesulfonic anhydride in mild conditions. This facile method affords a convenient way for the synthesis of other similar chiral derivatives.

Acknowledgements

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References and notes

- (1) Leek, H.; Andersson, S. *Molecules* **2017**, *22*, 158.
- (2) (a) Christmann, M.; Brase, S. *Asymmetric Synthesis II: More Methods and Applications* **2012**. (b) Walsh, P.; Kozlowski, M. *Fundamentals of Asymmetric Catalysis*; University Science Books: Sausalito, CA, **2009**.
- (3) Leek, H.; Thunberg, L.; Jonson, A. C.; Ohlen, K.; Klarqvist, M. *Drug discovery today* **2017**, *22*, 133–139.
- (4) Boland, S.; Bourin, A.; Alen, J.; Geraets, J.; Schroeders, P.; Castermans, K.; Kindt, N.; Boumans, N.; Panitti, L.; Fransen, S.; Vanormelingen, J.; Stassen, J. M.; Leysen, D.; Defert, O. *J. Med. Chem.* **2015**, *58*, 4309–4324.
- (5) Bhuniya, D.; Deshpande, A.; Kandalkar, S.; Kobal, B.; Vyavahare, V.; Kaduskar, R. Patent US 2012214735A1, **2012**.
- (6) Lehmann-lintz, T.; Kley, J.; Redemann, N.; Sauer, A.; Thomas, L.; Wiedenmayer, D.; Austen, M.; Danilewicz, J.; Schneider, M.; Schreiter, K.; Black, P.; Blackaby, W.; Linney, I. Patent WO 2011104337, **2011**.
- (7) Barker, S. A.; Brimacombe, J. S.; Foster, A. B.; Whiffen, D. H.; Zweifel, G. *Tetrahedron* **1959**, *7*, 10–18.
- (8) (a) Avi, M.; Fechter, M. H.; Gruber, K.; Belaj, F.; Poechlauer, P.; Griengl, H. *Tetrahedron* **2004**, *60*, 10411–10418. (b) Lopfe, M.; Linden, A.; Heimgartner, H. *Heterocycles* **2011**, *82*, 1267–1282. (c) Yamaguchi, A.; Hiyoshi, N.; Sato, O.; Shirai, M. *Top. Catal.* **2010**, *53*, 487–491. (d) Matteson, D. S. *Science of Synthesis* **2004**, *6*, 5–79. (e) Chini, M.; Crotti, P.; Gardelli, C.; Macchia, F. *Tetrahedron* **1994**, *50*, 1261–174. (f) Mihailovic, M. L.; Marinkovic, D. *Croat. Chem. Acta.* **1986**, *59*, 109–120. (g) Mihailovic, M. L.; Pavlovic, N.; Gojkovic, S. *Glasnik Hemijskog Društva Beograd* **1975**, *40*, 309–319. (h) Hartman, F. C.; Barker, R. *J. Org. Chem.* **1964**, *29*, 873–877.
- (9) Baldwin, J. J.; Claremont, D. A.; Tice, C. M.; Cacatian, S.; Dillard, L. W.; Ishchenko, A. V.; Yuan, J.; Xu, Z. R.; Mcgeehan, G.; Zhao, W.; Simpson, R. D.; Singh, S. B.; Flaherty, P. T.; Patent WO 2008036216, **2008**.
- (10) (a) Brown, H. C.; Gupta, A. K. *J. Organomet. Chem.* **1988**, *341*, 73–81. (b) Brown, H. C.; Prasad, J. V. N. V. *J. Org. Chem.* **1986**, *51*, 4526–4530. (c) Brown, H. C.; Bakshi, R. K.; Singaram, B. *J. Am. Chem. Soc.* **1988**, *5*, 1529–1534. (d) Brown, H. C.; Prasad, J. V. N. V. *J. Am. Chem. Soc.* **1986**, *108*, 2049–2054. (e) Brown, H. C.; Prasad, J. V. N. V.; Zee, S. H. *J. Org. Chem.* **1985**, *50*, 1582–1589. (f) Brown, H. C.; Joshi, N. N. *J. Org. Chem.* **1988**, *53*, 4059–4062. (g) Narayana, C.; Periasamy, M. *J. Chem. Soc., Chem. Commun.* **1987**, *24*, 1857–1859.
- (11) Wu, M. H.; Hansen, K. B.; Jacobsen, E. N. *Angew. Chem. Int. Ed.* **1999**, *38*, 2012–2014.
- (12) Savage, S.; Babu, S.; Zak, M.; Mao, Z.; Cao, J.; Ge, Y.; Ma, D.; Jiang, G. *Synlett* **2013**, *24*, 987–990.
- (13) Rajendran, R.; Savita, G.; Nagabushanam, K.; Muhammed, M. *Tetrahedron: Asymmetry* **2013**, *24*, 663–668.
- (14) Shiro, Y.; Kato, K.; Fujii, M.; Ida, Y.; Akita, H.; *Tetrahedron* **2006**, *62*, 8687–8695.
- (15) Ashoorzadeh, A.; Archibald, G.; Caprio, V. *Tetrahedron* **2009**, *65*, 4671–4680.

Highlights

- . (S)-3-hydroxytetrahydropyran was synthesized from inexpensive L-glutamic acid.
- . One step intramolecular etherification was promoted by Tf_2O under mild conditions.
- . The product was prepared with >95% ee in a gram-scale without recrystallization.