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A Highly Stereoselective Synthetic Method for cis-2-Hydroxymethyl-6-alkyltetrahydropyrans

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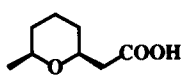
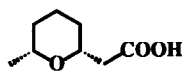
Intramolecular 1,4-addition, α,β-unsaturated sulfoxides, cis-2-hydroxymethyl-6-alkyltetrahydropyrans

Abstract: A highly stereoselective synthetic method for cis-2-hydroxymethyl-6-alkyltetrahydropyrans is described by an intramolecular 1,4-addition of alcohol to α,β-unsaturated sulfoxide as a key reaction. This method is applied to syntheses of (+)- and (-)-(cis-6-methyltetrahydropyran-2-yl)acetic acids.

Substituted tetrahydropyrans are an important class of compounds for polyether synthesis.[1] Recently, (+)-(cis-6-Methyltetrahydropyran-2-yl)acetic acid(**1a**),[2] a constituent of the perfume material civet, a glandular secretion of the civet cat (*Viverra civetta*) has attracted much attention owing to its synthetically interesting cis-2,6-disubstituted tetrahydropyran skeleton. More than 20 routes to this compound including asymmetric syntheses have been reported so far.[3c] However, there have appeared very few general methodologies on the highly stereoselective generation of cis-2,6-disubstituted tetrahydropyran skeletons.



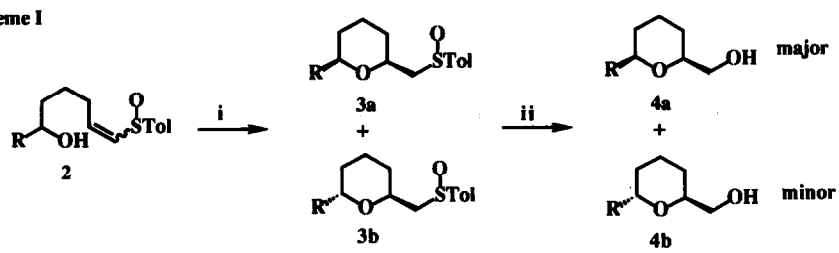
1a



1b

In our continuous studies on 1,4-addition of alcohol to α,β-unsaturated sulfoxide,[4] we wanted to develop a new synthetic method for cis-2,6-disubstituted tetrahydropyrans by an intramolecular 1,4-addition of α,β-unsaturated sulfoxide **2**.[5,6] In the event, we were pleased to find that cis-2-(*p*-tolylsulfinyl)methyl-6-alkyltetrahydropyran **3a** can be obtained from **2** with high stereoselectivity under thermodynamically controlled conditions as shown in Scheme I. We wish to report here a highly stereoselective synthesis of cis-2-hydroxymethyl-6-alkyltetrahydropyran **4a** and its application to the enantioselective syntheses of (+) and (-)-(cis-6-methyltetrahydropyran-2-yl)acetic acids(**1a**) and (**1b**).

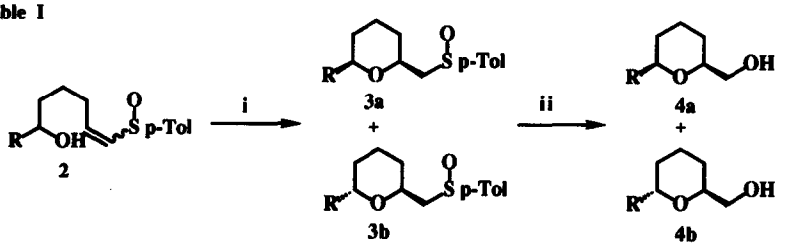
Scheme I



(i) NaH(5eq)/THF/50°C (ii) Ac_2O/NaOAc, $LiAlH_4$/THF

The intramolecular 1,4-addition of **2** was surveyed under thermodynamically controlled conditions. When the sulfoxides **2** were subjected to the intramolecular 1,4-addition at room temperature in the presence of NaH(5 eq), the stereoselectivity for cis **3a** was not high(runs 1, 2, 5, 6).[7] But it was remarkably improved at higher temperature. The highest stereoselectivity was observed at 50 °C(runs 4, 8, 10, 12).[8] Prolonged reaction time over 24 h at 50 °C decreased gradually both the selectivity and yields of **3** due to their decomposition. Both the stereoselectivity and yields of **3** were determined after conversion to the alcohols **4a** and **4b**. These results are listed in Table I.

Table I

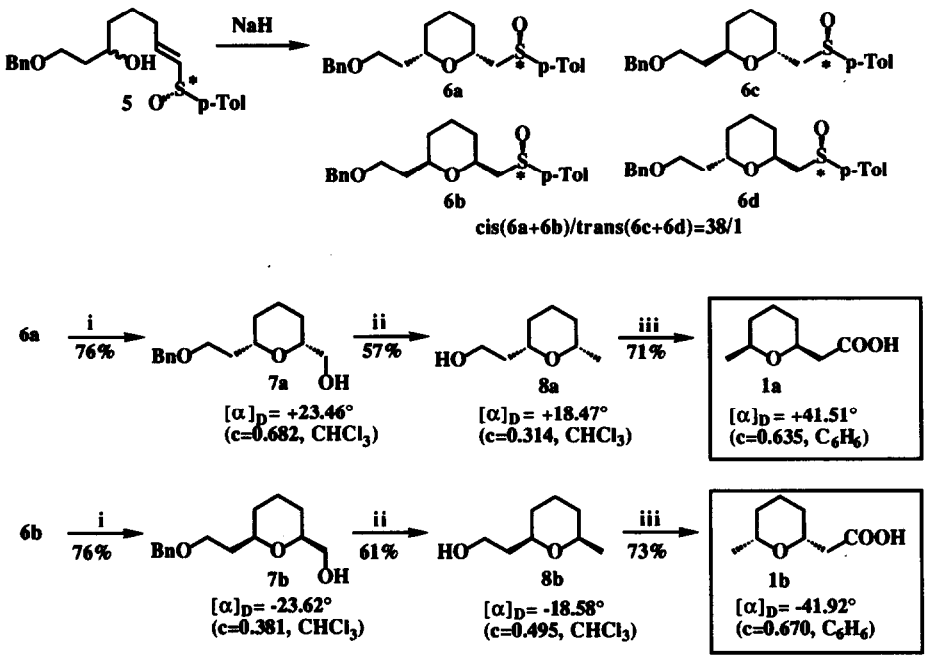


(i) NaH(5 eq)/THF (ii) Ac_2O/NaOAc/100 °C, $LiAlH_4$/THF

Run	R	Vinyl sulfoxide	Temp	Time(h)	cis/trans[a] 4a/4b	Yield(%)[b] 4a + 4b
1	Ph-CH=CH-	E	r.t.	18	8/1	67
2		Z	r.t.	18	2/1	58
3		Z/E=4/6	50°C	6	12/1	58
4		Z/E=4/6	50°C	12	18/1	78
5	n-C_5H_{11}-	E	r.t.	18	7/1	76
6		Z	r.t.	18	1/1	74
7		Z/E=4/6	50°C	6	34/1	79
8		Z/E=4/6	50°C	12	35/1	80
9	CH_3-CH=CH-	Z/E=4/6	50°C	12	2/1	67
10		Z/E=4/6	50°C	24	25/1	60
11	Ph-	Z/E=4/6	r.t.	18	66/1	85
12		Z/E=4/6	50°C	12	71/1	83

a) Stereoselectivity was determined by GLC(capillary column 0.3 mm x 25 m) or HPLC.
b) Combined yield by a short flash column chromatography on silica gel.

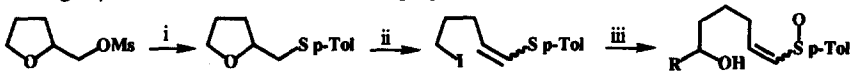
The present method was nicely applied to the synthesis of both (+)- and (-)-(cis-6-methyltetrahydropyran-2-yl)acetic acids. Optically active *p*-tolylsulfoxide **5**[9] was treated with NaH (5.0 eq) in THF at 50 °C for 20 h to give a mixture of four diastereomers (**6a-6d**) in 90% combined yields. The most polar cis **6a**(45.2%) and the least polar cis **6b**(42.5%) were easily isolated by flash column chromatography on silica gel. However, **6c** and **6d** could not be separated each other(2.3% combined yield). The ratio of **6a**/**6b**(ca.1/1) was reasonable because the starting sulfoxide **5** was a mixture of two epimers with respect to the hydroxy group. Thus, the ratio of cis (**6a** + **6b**)/trans(**6c** + **6d**) was 38 /1). Then, **6a** was subjected to Pummerer rearrangement (Ac_2O/NaOAc/100 °C/12 h), and ensuing reduction($LiAlH_4$/THF/rt), providing the alcohol **7a**(76%). Also, **6b** was converted to **7b**(76%) in the same manner. The alcohol **7a** was transformed into the alcohol **8a**(57%) by a sequence of mesylation(MsCl/Et_3N), reduction($LiAlH_4$/THF/refl.), and hydrogenolysis(Pd/C in EtOH). By the same way, **7b** was also converted to **8b** (61%). Finally, oxidation of **8a** (CrO_3/acetone/0 °C) gave the carboxylic acid **1a**[10](71%, $[\alpha]^{17}_D$ +41.51°, c 0.635, C_6H_6: lit.,[3a] $[\alpha]^{17}_D$ +43.85°, c 2.52, C_6H_6: lit.,[3c] $[\alpha]^{17}_D$ + 42.3°, c 0.84, C_6H_6). Similarly, **8b** was converted to **1b**[10] (73%, $[\alpha]^{17}_D$ -41.92°, c 0.670, C_6H_6: lit.,[3b] $[\alpha]^{17}_D$ -40.8, c 1.0, C_6H_6). The specific rotation values and NMR spectra (^{1}HNMR: 400MHz, ^{13}C NMR: 100 MHz) of **1a** and **1b** were fully identical with those reported.[3a, 3b]



(i) Ac_2O/NaOAc, $LiAlH_4$/THF (ii) MsCl/Et_3N, $LiAlH_4$/THF, H_2/Pd/C (iii) CrO_3/acetone

References and Notes

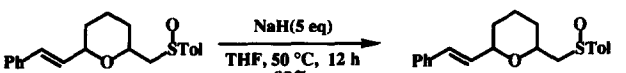
1. Boivin, T. L. B. *Tetrahedron* **1987**, *43*, 3309.
2. Maurer, B.; Grieder, A.; Thommen, W. *Helv. Chim. Acta* **1979**, *62*, 44.
3. (a) Keinan, E.; Seth, K. K.; Lamed, R. *J. Am. Chem. Soc.* **1986**, *108*, 3474. (b) Kotsuki, H.; Ushio, Y.; Kadota, I.; Ochi, M. *Chem. Lett.*, **1988**, 927. (c) Kotsuki, H. *Synlett* **1992**, 97 and references cited therein.
4. (a) Mandai, T.; Ueda, M.; Hasegawa, S.; Kawada, M.; Tsuji, J.; Saito, S. *Tetrahedron Lett.* **1990**, *31*, 4041. (b) Mandai, T.; Matsumoto, S.; Kohama, M.; Kawada, M.; Tsuji, J.; Saito, S. *J. Org. Chem.* **1990**, *55*, 5671.
5. The starting α,β-unsaturated sulfoxide **2** was prepared as follows.



Z/E=4/6 **2**

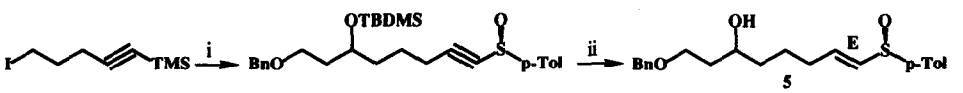
(i) p-TolSH/NaOH/EtOH 94% (ii) n-BuLi/THF 90%, TsCl/Py, NaI/acetone 84%
(iii) t-BuLi/RCHO/Et_2O 75-90%, m-CPBA 85-92%.

6. Spiroketals were synthesized by an intramolecular 1,4-addition of alcohol to cyclic α,β- unsaturated sulfoxide. Iwata, C.; Hattori, K.; Uchida, S.; Imanishi, T. *Tetrahedron Lett.* **1984**, *25*, 2995.; Iwata, C.; Fujita, M.; Hattori, K.; Uchida, S.; *ibid.* **1985**, *26*, 2221.
7. The intramolecular 1,4-addition of **2** under kinetically controlled conditions, i.e., in the presence of a catalytic to stoichiometric amounts of NaH(0.3-1.2 eq) at room temperature for 3h gave unsatisfactory results. Stereoselectivity (**4a/4b**) from E isomer of **2** was found to be 2.5-4.8/1, however, no stereoselectivity was generally observed in the case of Z isomer.
8. Isomerization of trans **3b** to cis **3a** by an elimination-addition sequence was confirmed by the following experiment.



c/t=3.3/1 c/t=17.5/1

9. Optically active sulfoxide **5** was prepared according to the literature: Kosugi, H.; Kitaoka, M.; Tagami, K.; Takahashi, A.; Uda, H. *J. Org. Chem.* **1987**, *52*, 1078.



5

(i) t-BuLi/BnO$(CH_2)_2$CHO/Et_2O 70%, K_2CO_3/MeOH 90%, TBDMSCl/DMF 92% (c) EtMgBr, (-)-Menthyl (-)-(S)-p-toluenesulfinate/Et_2O/toluene 78% (ii) DIBAL/toluene/-83°C, HF-Py/CH_3CN 83%.

10. The optical purity of **1a** and **1b** was determined according to the literature; Maurer, B.; Thommen, W. *Helv. Chim. Acta* **1979**, 62, 1096. The ^1H NMR (400 MHz) spectra of the methyl esters of **1a** and **1b** in the presence of Eu(HFC)$_3$ (molar ratio of shift reagent/ester: 0.1-0.5) showed only one set of signals. The ^1H NMR spectra of the racemic methyl ester measured in the same manner showed the methyl(a pair of doublet) and methyl ester signals(a pair of singlet). Thus, the optical purity of the carboxylic acids **1a** and **1b** was determined to be over 95%.

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