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Technical Notes

A Convenient Practical Method for the Preparation of (−)-(1*S*,2*S*)-5-Norbornene-2-carboxylic Acid, Incorporating Efficient Recovery of the Chiral Auxiliary D-Pantolactone

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Abstract:

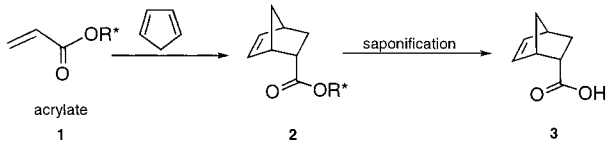
A convenient practical method was developed for the preparation of enantiomerically pure (−)-(1*S*,2*S*)-5-norbornene-2-carboxylic acid, wherein the chiral auxiliary D-pantolactone was recovered efficiently.

Introduction

Enantiomerically pure (−)-(1*S*,2*S*)-5-norbornene-2-carboxylic acid (**3**), a key intermediate in the synthesis of some adenosine receptor antagonists,[1] has generally been prepared by Diels−Alder reaction of cyclopentadiene with a chiral auxiliary functionalized acrylate (**1**), followed by saponification (see Scheme 1). Choosing a suitable chiral auxiliary has been the focus of many researchers. Even though dihydroxylated dispiroketal,[2] *cis*-1-arylsulfonamido-2-indanols,[3] and (*R*)-(−)-1-mesityl-2,2,2-trifluoroethanol[4] can all be used as chiral auxiliaries with recovery incorporated, they are not suitable for large-scale manufacture because they can use tedious procedures, harsh conditions, or expensive precursors.

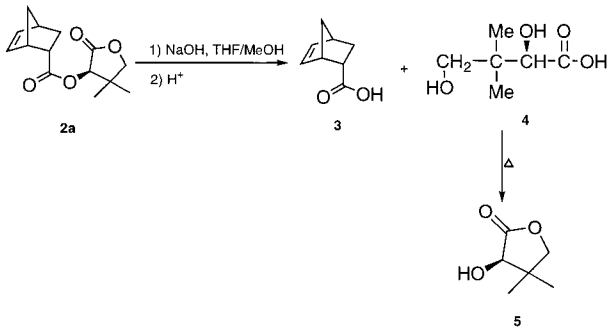
Poll et al. reported using D-pantolactone, a readily available commercial reagent, as a chiral auxiliary in the preparation of (−)-(1*S*,2*S*)-5-norbornene-2-carboxylic acid (**3**),[5] and they observed that the associated Diels−Alder reaction proceeded with very high *endo*-diastereoselectivity. Subsequent hydrolysis of the recrystallized Diels−Alder adduct was carried out with lithium hydroxide in THF/water at room temperature for 26 h. Then THF was evaporated in vacuo, and the remaining aqueous solution was acidified and extracted with *n*-pentane/CH_2Cl_2. After drying of the organic extract with sodium sulfate and evaporation of solvents, the product (−)-(1*S*,2*S*)-5-norbornene-2-carboxylic acid (**3**) was obtained in 97% yield.

Scheme 1



R*OH: chiral auxiliary

Scheme 2



Results and Discussion

Using Poll's method as a basis for process development, three significant modifications have been achieved. The new procedure to prepare (−)-(1*S*,2*S*)-5-norbornene-2-carboxylic acid (**3**) is convenient and practical. In addition, the most costly chiral auxiliary, D-pantolactone (**5**), was recovered efficiently (see Scheme 2).

Modification 1: Reduced Hydrolysis Reaction Time to 1 h. To enhance the solubility of Diels−Alder adduct **2a** in the reaction system, methanol was added to the reaction mixture, which then became homogeneous. Using NaOH−H_2O/THF−MeOH instead of the originally reported LiOH−H_2O/THF reduced the reaction time for the hydrolysis from 26 to 1 h.

Modification 2: A Simpler Workup of (−)-(1*S*,2*S*)-5-Norbornene-2-carboxylic Acid. Advantage was taken of the higher water solubility of pantoic acid **4** and the low water solubility of the product **3** by first evaporation of organic solvents. Then, after acidification with 4 N HCl and cooling in an ice bath, the product, (−)-(1*S*,2*S*)-5-norbornene-2-carboxylic acid (**3**), was precipitated and could be collected by filtration. For plant operation, this was more acceptable

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(2) Bezuidenhoudt, B. C. B.; Castle, G. H.; Geden, J. V.; Ley, S. V. *Tetrahedron Lett.* **1994**, *35*, 7451−7454.
(3) Ghosh, A. K.; Mathivanan, P. *Tetrahedron: Asymmetry* **1996**, *7*, 375−378.
(4) Corey, E. J.; Cheng, X. M.; Cimprich, K. A. *Tetrahedron Lett.* **1991**, *32*, 6839−6842.
(5) Poll, T.; Sobczak, A.; Hartmann, H.; Helmchen, G. *Tetrahedron Lett.* **1985**, *26*, 3095−3098.

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than the reported *n*-pentane/CH_2Cl_2 extraction, drying, and evaporation.

Modification 3: Efficient Recovery of the Chiral Auxiliary D-Pantolactone (5). D-Pantolactone, the cost driver of the whole synthesis, has been widely used as an efficient chiral auxiliary in asymmetric syntheses.[6,7] However, few literature references actually mention the recovery of D-pantolactone, except for one dated 1940, where D-pantolactone was obtained from a liver extract by a complicated procedure.[8]

Since, in Poll's method, the D-pantolactone fragment was hydrolyzed to the ring-opened, water-soluble D-pantoic acid (**4**), several methods were tried in our laboratory to keep the pantolactone portion intact during the removal of the chiral auxiliary from the substrate. Mild hydrolysis with K_2CO_3/CH_3OH at room temperature or in an ice bath and *trans*-esterification[9] did not succeed. This indicated that the carbonyl carbon of the lactone was attacked preferentially.

Therefore, an attempt to close the ring of D-pantoic acid (**4**) to a five-membered lactone ring by simple heating of the acidified mixture was tried, and this proved to be successful. The lactonization is an intramolecular nucleophilic attack by the γ-hydroxy group on the protonated carboxylic acid, which should not cause racemization.

Using modified reaction conditions as shown in Scheme 2, the Diels−Alder adduct **2a** was hydrolyzed to give, after acidification to pH 2−3, (−)-(1*S*,2*S*)-5-norbornene-2-carboxylic acid (**3**) and D-pantoic acid (**4**). The product **3** was collected by filtration as described in modification 2. The filtrate containing the D-pantoic acid was then heated at 90−95 °C for 2−3 h to complete the lactonization, and after cooling, sodium bicarbonate was added to bring the pH to 7.5−8. Under these slightly basic conditions, a small amount of (−)-(1*S*,2*S*)-5-norbornene-2-carboxylic acid (**3**) was retained in the aqueous phase as a salt without mixing with the subsequent D-pantolactone extract. Strongly basic conditions would have decomposed the D-pantolactone molecule and were, therefore, avoided. After this turbid, slightly basic mixture was filtered, the filtrate was extracted with ethyl acetate. Subsequent drying and concentration produced recycled D-pantolactone (**5**) as a pure white crystalline solid in a high recovery of 85%. For convenient plant operation, after two-thirds of the ethyl acetate was removed, the product D-pantolactone (**5**) can be precipitated as crystals by addition of heptane and can, therefore, be collected by filtration. The optical purity of D-pantolactone can be increased by recrystallization from methyl *tert*-butyl ether/heptane. Nevertheless, it is wise to use a solution of D-pantolactone extract directly in acrylate formation, and it is worthwhile to do further investigation.

All analytical data for the recycled D-pantolactone conformed to the theoretical data or were identical to those of commercially available D-pantolactone.

Key features of the modified procedure were the following:

(i) D-Pantolactone, which is quite water soluble, was recovered in a yield of up to 85% by extracting with ethyl acetate four times. Additional extraction time can increase the amount of recovered product. Furthermore, if a continuous extraction apparatus were used in manufacturing, the recovery yield could be even higher. In consideration of the whole procedure, 0.53 g of D-pantolactone can be recovered if 1 g of D-pantolactone is used in the formation of acrylate.[10]

(ii) Detailed HPLC and optical rotation analyses (see Experimental Section) indicated that no racemization had occurred during this process, and D-pantolactone could, therefore, be recycled repeatedly without reducing its optical purity.

(iii) Lactonization was also possible at room temperature overnight, indicating that the reaction proceeded easily. It will be significant to do further experiments and to apply this room-temperature lactonization to plant operation.

We noted that, in d_6-DMSO, D-pantolactone (**5**) decomposed quickly to form D-pantoic acid (**4**). The ^{1}H NMR of compound **5** recorded in d_6-DMSO actually reflected the structure of D-pantoic acid (**4**) (see Experimental Section). The commercial D-pantolactone behaves in the exact same way.

Conclusions

A convenient, cost-effective procedure to prepare (−)-(1*S*,2*S*)-5-norbornene-2-carboxylic acid (**3**) has been developed and successfully scaled up to kilogram scale in a pilot plant. The efficient method presented above to recycle D-pantolactone may be applicable to other reactions where D-pantolactone is used as a chiral auxiliary.

Experimental Section

Melting points were determined on an Electrothermal digital melting point apparatus (IA9300). NMR spectra were measured on a Bruker spectrometer (300 MHz). Elemental analysis was performed by QTI, Whitehouse, NJ. Optical rotations were obtained on a Perkin-Elmer polarimeter 241. HPLC analyses were performed on an Alliance Waters 2690 separations module system with a Waters 996 photodiode array detector. The chemical purity of (−)-(1*S*,2*S*)-5-norbornene-2-carboxylic acid (**3**) and D-pantolactone **(5**) was measured by reversed-phase HPLC using a Keystone BDS Hypersil C8 column (150 × 2.0 mm, 5 μm). The chiral purity of (−)-(1*S*,2*S*)-5-norbornene-2-carboxylic acid (**3**) and D-pantolactone **(5**) was measured by normal-phase HPLC using a Chiralcel OD column (250 × 4.6 mm, 10 μm).

Preparation of (−)-(1*S*,2*S*)-5-Norbornene-2-carboxylic Acid (3). To a stirred solution of Diels−Alder adduct **2a** (275.7 g, 1.1 mol) in THF (1100 mL) and MeOH (550 mL) was added 5 N NaOH (1100 mL) dropwise. The resulting colorless mixture was stirred at room temperature for 1 h, and the mixture was concentrated in vacuo in a water bath set at 35−45 °C to remove organic solvents. The residue

(6) Poll, T.; Abdel Hady, A. F.; Karge, R.; Linz, G.; Weetman, J.; Helmchen, G. *Tetrahedron Lett.* **1989**, *30*, 5595.
(7) Linz, G.; Weetman, J.; Abdel Hady, A. F.; Helmchen, G. *Tetrahedron Lett.* **1989**, *30*, 5599−5602.
(8) Stiller, E. T.; Keresztesy, J. C.; Finkelstein, J. *J. Am. Chem. Soc.* **1940**, *62*, 1779.
(9) This experiment was carried out by Chemical Research Lab., Biogen.
(10) Calculated as 80% yield for acrylate formation, 79% yield for Diels−Alder reaction, and 85% yield for D-pantolactone recovery from compound **2a**.

was then placed in an ice bath, and 4 N HCl was added dropwise to a pH of 2−3. The resulting white slurry was stirred for 0.5 h in the ice bath and then filtered by suction (the filtrate was kept for recycling D-pantolactone). The filter cake was washed with a small amount of cold water and dried to give the product as a white solid: yield 135 g (89%); mp 40.5−41.3 °C; 99% HPLC chemical purity (eluant A, 25 mM $NaH_2PO_4 \cdot H_2O$ in HPLC grade water; eluant B, 50% 50 mM $NaH_2PO_4 \cdot H_2O$ in HPLC grade water + 50% acetonitrile; gradient, 70% A → 30% A and 30% B → 70% B 0−10 min, 30% A → 0% A and 70% B → 100% B 10−20 min; UV detection at 205 nm); 100% HPLC chiral purity (eluant, 10% 2-propanol + 90% hexane; UV detection at 205 nm); $[\alpha]^{25}_D$ −151.5 (*c* 2.0, $CHCl_3$), $[\alpha]^{25}_D$ −144.53 (*c* 1.5, 90.5% EtOH), [lit.[5] $[\alpha]^{20}_D$ −146.9 (*c* 3.0, 95% EtOH)]; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.26 (d, 1H, $C_{7b}H$), 1.39 (m, 2H, $C_{3b}H$ + $C_{7a}H$), 1.89 (m, 1H, $C_{3a}H$), 2.89 (s, 1H, C_4H), 2.97 (dt, 1H, C_2H), 3.21 (s, 1H, C_1H), 5.97 (dd, 1H, C_5H), 6.18 (dd, 1H, C_6H), 10.60 (s, br, 1H, −COOH).

Recycle of D-Pantolactone (5). The above aqueous filtrate from the isolation of (−)-(1*S*,2*S*)-5-norbornene-2-carboxylic acid (**3**) was heated in a water bath (90−95 °C) for 2−3 h. After the filtrate was cooled to ambient temperature, $NaHCO_3$ powder was added slowly to a pH of 7.5−8. The turbid mixture was then filtered and extracted four times with ethyl acetate (4 × 250 mL), and the combined organic extracts were dried with Na_2SO_4 and concentrated to give D-pantolactone (**5**) as a white crystalline solid: yield 122 g (85%); mp 92.2−93.2 °C (lit.[11] mp 92 °C); 98.98% HPLC chemical purity (eluant, 90% 50 mM $NaH_2PO_4 \cdot H_2O$ in HPLC grade water + 10% acetonitrile; UV detection at 205 nm); 100% HPLC chiral purity (eluant, 10% 2-propanol + 90% hexane; UV detection at 205 nm) [the chemical and chiral HPLC purities for commercial D-pantolactone are 99.41% and 100%, respectively]; $[\alpha]^{25}_D$ −46.188 (*c* 1.7, H_2O) [the optical rotation measured for commercial D-pantolactone[12] was $[\alpha]^{25}_D$ −47.208 (*c* 1.7, H_2O)]; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.07 (s, 3H, $-CH_3$), 1.19 (s, 3H, $-CH_3$), 3.18 (s, 1H, −OH), 3.90 (d, ^2J = 9.18 Hz, 1H, C−H), 3.99 (d, ^2J = 9.18 Hz, 1H, C−H), 4.11 (s, 1H, OH−C−*H*); ^{13}C NMR (300 MHz, $CDCl_3$) δ 178.05, 76.38, 75.50, 40.65, 22.64, 18.73; ^{1}H NMR (300 MHz, DMSO) δ 0.88 (s, 3H, $-CH_3$), 1.06 (s, 3H, $-CH_3$), 3.90 (s, 2H, $-CH_2$), 4.07 (d, J = 6.00 Hz, 1H, OH−C-*H*), 5.94 (d, J = 6.00 Hz, 1H, *H*O−C−H). After addition of D_2O, the signal at 5.94 ppm disappeared and the doublet at 4.07 ppm collapsed to a single peak. Anal. Calcd for $C_6H_{10}O_3$: C, 55.38; H, 7.69. Found: C, 55.47; H, 7.61.

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(11) *The Merck Index*; Merck & Co.: Rahway, NJ, 1996; Vol. 12, p 7145.
(12) D-(−)-Pantoyl lactone, purchased from Sigma (Product No. P 2625), St. Louis, MO.