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Removal of Pinanol via Continuous Steam Distillation

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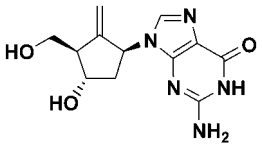
Abstract:

A practical procedure for the efficient removal of pinanol from the reaction mixture has been developed. The process was based on the observation that pinanol can be easily removed by steam distillation in the laboratory. On-scale, a continuous counter-current column stripper was implemented to remove pinanol.

The chiral hydroboration−oxidation sequence developed by the Brown group is one of the most powerful and commonly used protocols to prepare chiral alcohols from olefins.[1] Although this protocol has been used extensively, the major limitation to this approach, especially on-scale, is the generation of undesired chiral pinanol as the byproduct. Pinanol, a high boiling liquid (bp 219 °C), can be removed by steam distillation, but the process is ***very tedious*** and ***slow*** and is often a serious ***pratical problem which hinders the application of this protocol*** on-scale. In connection with our efforts to prepare clinical supplies of entecavir, a novel carbocylic 2′-deoxyguanosine analogue with potent and selective anti-HBV activity, the need arose to remove pinanol on scale. This report describes a practical procedure to remove pinanol by continuous steam distillation. Entecavir has been asymmetrically synthesized in 10 steps in 18% overall chemical yield and >99% optical purity.[2]



Entecavir

The synthesis of entecavir uses the known chiral cyclopentyl epoxide (**III**),[3] which is prepared in a few steps starting from readily available sodium cyclopenadienide (CpNa). The synthesis of epoxide (**III**) from sodium cylcopentadienide is outlined below in Scheme 1.

The first intermediate **I** is prepared by alkylation of CpNa with benzyloxymethyl chloride (BOMCl), followed by chiral hydroboration−oxidation of the alkylated BOMCp (Scheme 2). Intermediate **I** possesses ***two of the three chiral centers*** of entecavir and also sets up the introduction of the desired epoxide, which affords the final chiral center.

The asymmetric hydroboration followed by oxidation gives a crude reaction mixture which contains the desired alcohol (**I**), pinene, benzyl alcohol, and chiral pinanol. The optimum amount of the chiral hydroborating agent used for hydroboration of BOMCp was 1.5 equiv, thereby generating nearly 3 equiv of chiral pinanol as an unwanted byproduct. The presence of such high levels of pinanol interferes in the successful epoxidation of **I**. Thus, the pinanol had to be removed or its levels lowered significantly prior to the epoxidation−esterification step, which affords **II** as the first solid isolated intermediate in the synthesis (see Table 1).

Table 1. **Preparation of crude I**

mol of CpNa	crude oil (**I**) kg	amount of **I** by HPLC quantitation kg
14.3	9.5	1.7
119.7	159	15.6
108.6	138	14.5

Table 2. **Pinanol removal and isolation of I**

before pinanol removal oil/HPLC quantitation kg/kg	time spent in pinanol removal h	after pinanol removal oil/HPLC quantitation kg/kg	overall yield %
9.5/1.7	16[a,c]	3.3/1.3	45
159/15.6[a]	91[a]	24.2/12.1	49[c]
138/14.5[a]	32[a,b]	16.3/13[d]	59[c]

[a] The ratio of pinanol to **I** at the beginning of the distillation was 17:1, and it was lowered to a final ratio of 1:16 at the end of the distillation. [b] In this batch, a 12-in. diameter Schott column was used, compared to a 3-in. column in the previous two runs, thereby significantly reducing the removal time. The operating parameters are as follows:

3" column, 45.6 cm^2 cross sectional area	12" column, 730 cm^2 cross sectional area
Feed flow rate is 0.53 Kg/min	Feed flow rate is 6.3 Kg/min
Steam flow rate is 0.164 Kg/min	Steam Flow rate is 2.2 Kg/min.
Ratio 3.23 Kg feed/Kg steam	Ratio is 2.84 Kg feed/Kg steam

[c] In these batches, crude oil of **I** was subjected to Darco G-60 treatment after pinanol removal. [d] The quality of isolated **I** was dependent on two factors. The quality of the supplied CpNa from the vendor and the efficiency of the continuous steam distillation. The quality of the CpNa for the last batch was the best, and the use of the larger-diameter column with specialized Pro-pak packing greatly improved the efficiency of the column in the steam distillation and hence resulted in a better quality product (**I**) in the last run.

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(1) (a) Brown, H. C.; Pelter, A.; Smith, K. *Borane Reagents*; Academic Press: 1988. (b) Brown, H. C. *Organic Synthesis via Boranes*; Wiley-Interscience Publication, 1975. (c) Brown, H. C. *Boranes in Organic Chemistry*; Cornell University Press: 1972 and references therein. (d) Brown, H. C.; Zweifel, G. *J. Am. Chem. Soc*. **1964**, *86*, 393 (e) Brown, H. C.; Zweifel, G.; Ayyangar, N. R. *J. Am. Chem. Soc*. **1964**, *86*, 397.

(2) Bisacchi, G. S.; Caho, S. T.; Bachard, C.; Daris, P.; Innaimo, S.; Jacobs, G. A.; Kocy, C.; Lapointe, P.; Martel, A.; Merchant, Z.; Slusarchyl, W. A.; Sundeen, J. E.; Young, M. G.; Colonno, R.; Zahler, R. *Bioorg. Med. Chem.* **1997**, 127.

(3) (a) Biggadike, K.; Borthwick, A. D.; Evans, D.; Exall, A. M.; Kirk, B. E.; Roberts, S. M.; Stephenson, L.; Youds, P. *J. Chem. Soc., Perkin Trans. 1* **1988**, 549. (b) Altmann, K.-H.; Kesselring, R. *Synlett* **1994,** 853. (c) Ezzitouni, A.: Barchi, J. M., Jr.; Marquez, V. E. *J. Chem. Soc., Chem. Commun.* **1995,** 1345. The methodology outlined to prepare **I** was originally developed by Partridge, J. J.; Chadha, N. K.; Uskokovic, M. R. *J. Am. Chem. Soc*. **1973,** *95*, 532.

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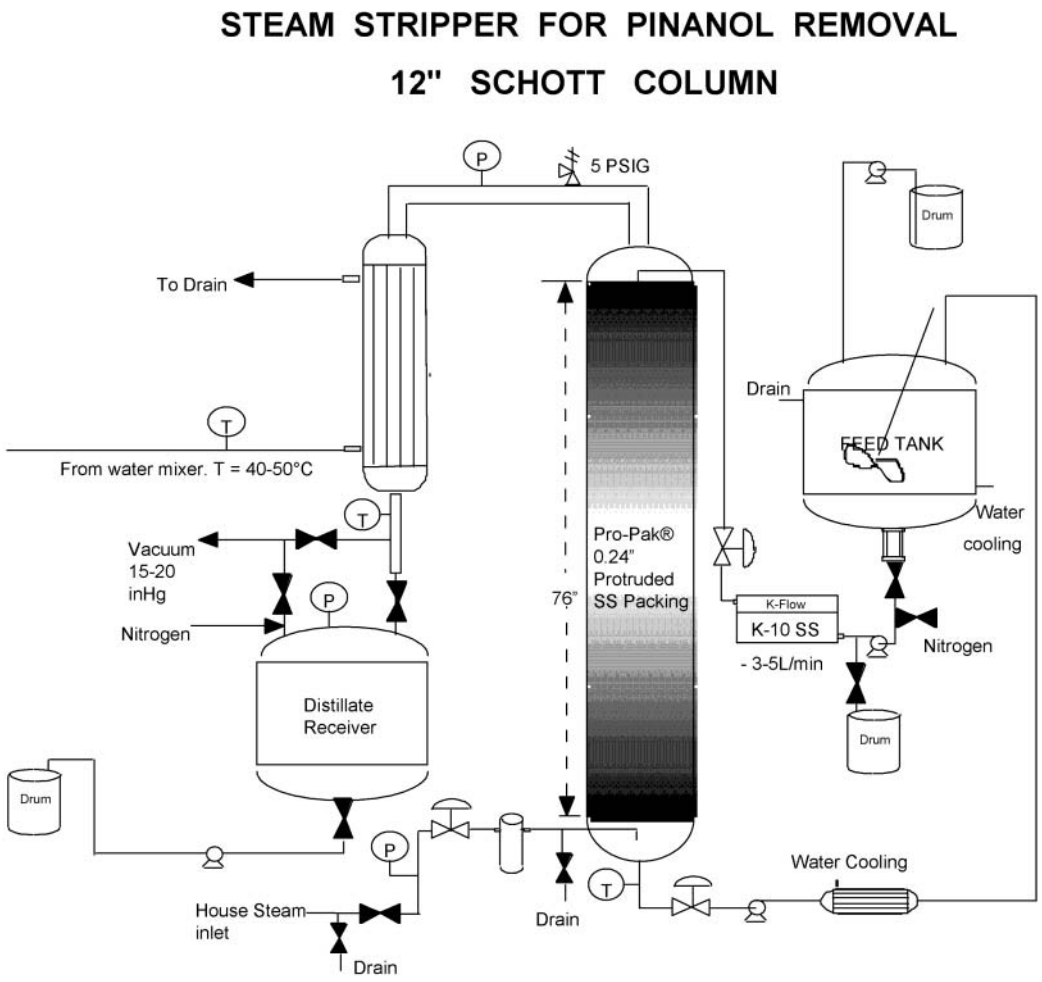
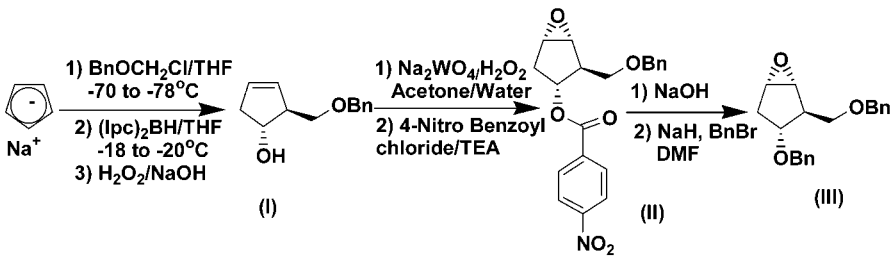


Figure 1.

Scheme 1

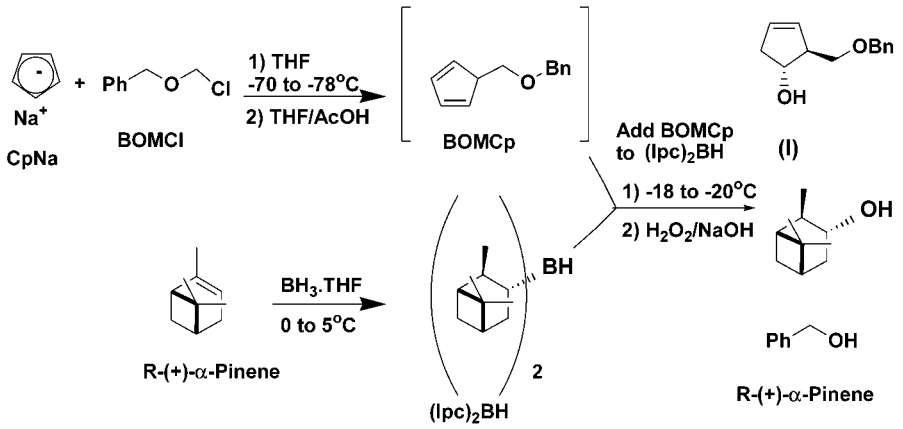


Earlier efforts to isolate intermediate **I** as a golden-colored oil involved distillation of the low-boiling components on a rotary evaporator, followed by repeated short-path distillation of the enriched material at 0.01−0.001 mm at 128 °C. The scale-up of this approach requires the purchase of specialized short-path wiped-film distillation equipment with a long lead time.

In the laboratory, it was observed that the levels of pinanol were significantly lowered by a simple steam distillation of the crude reaction mixture by continuously charging water to the reaction mixture and distilling water at 86−90 °C under a vacuum of ∼50 mmHg. This protocol would routinely generate a dark oil with pinanol levels of at 3−7%. These levels of pinanol were well tolerated in the epoxidation−esterification step. The crude oil **I** was dissolved in methanol, and the methanol solution was refluxed in the presence of Darco G-60 for 1 h. This procedure resulted in a nearly colorless solution of **I** with <1% loss, during the Darco treatment. The methanolic solution of **I** was solvent-exchanged into water for the epoxidation−esterification sequence.

Although steam distillation was successful on laboratory scale, it was not practical for scale-up, and hence an efficient process using a continuous-counter current steam distillation was developed (Figure 1). Attempts to remove pinanol in a single pass were tried in a 3-in. i.d. Scott glass column but proved unfeasible due to the high amounts of pinanol present in the crude oil (See note 1). A 12-in. i.d. Schott glass column was packed with Pro-Pak 0.24-in. protruded stainless steel random packaging. Steam was introduced from the bottom of the column, and the column was maintained constantly at ∼90 °C prior to the charge of the reaction mixture. Crude reaction mixture from a feed tank was continuously introduced from the top of the Schott column. The feed rate of

Scheme 2



the crude mixture was adjusted to maintain good turbulence and avoid any channeling during the steam distillation. This counter-current mixing allowed for removal of volatiles which were condensed and collected in the distillate receiver (See note 2). The order of removal of the volatiles was pinene, followed by benzyl alcohol, and finally pinanol. The enriched crude reaction mixture was collected at the bottom of the Schott column and was continuously recycled to the feed tank. The process was performed until the desired level of 3−7% of pinanol was attained in the crude oil of **I**. Removal of all the volatiles was monitored by periodically analyzing the enriched crude reaction mixture using a GC assay. The removal of volatiles increased the viscosity of the reaction mixture, and hence, constant adjustment by lowering the feed rate of the crude mixture was done to prevent the column from flooding. The formation of a dark oil indicated some degradation of product due to long distillation times. Use of a wider column reduced the distillation time (see distillation times and yields, for example, 2 and 3 in Table 2 below). This protocol efficiently provides improved recovery and cleaner quality of **I**, which is easily transformed to **II** as a white solid. The overall yield of **II** from CpNa was about 55%.

Summary of Pilot Plant Results to Prepare I

Notes. *(1)* To obtain a high turbulence in the column we had the feed ratio higher than we needed for a single pass, and hence we recirculated the crude oil. Building constraints prevented us from building a taller column.

(2) Greater than 90% of pinanol was recovered from the receiver. The condensor was maintained at a higher temperature to avoid freezing of the pinanol. The receiver was kept at 0−5 °C to trap the pinanol, although some pinanol was evident in the vacuum line.

Acknowledgment

We appreciate the assistance of Dr. Melanie Miller and Mr. David J. Kacsur during the on-scale implementation of the steam distillation. We also thank Mr. Min Lin and the New Brunswick Pilot plant Operations group for the successful implementation of **I** to **II** in the pilot plant.

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