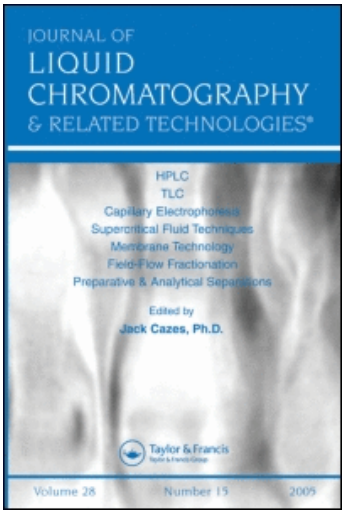

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Use of the Peak Shaving-Recycle Technique for Separation of Labdadiene and Labdatriene Isomers by HPLC

Subramaniam Mohanraj[a]; Werner Herz[a]
[a] Department of Chemistry, The Florida State University, Tallahassee, Florida

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USE OF THE PEAK SHAVING-RECYCLE TECHNIQUE FOR SEPARATION OF LABDADIENE AND LABDATRIENE ISOMERS BY HPLC

Subramaniam Mohanraj and Werner Herz

Department of Chemistry, The Florida State Universi
Tallahassee, Florida 32306

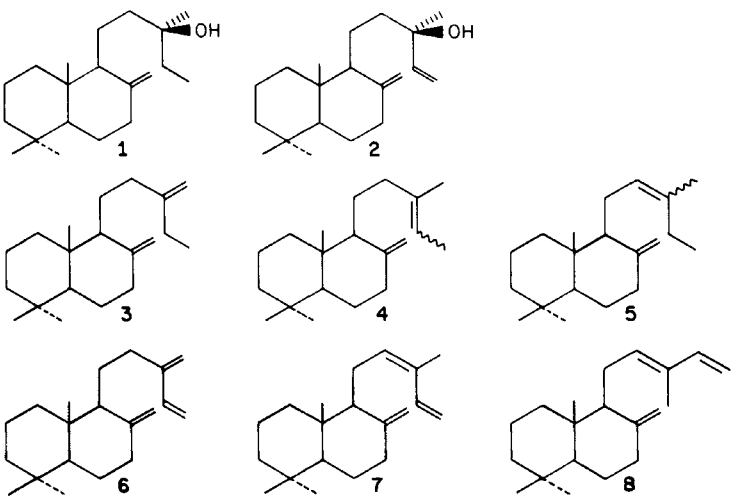
ABSTRACT

Separation on a preparative scale of labdadiene and labdatriene isomers by extensive use of the peak shaving-recycle technique is described. The procedure can be used to effect rapid and high yield separations of closely related isomers with $\alpha \sim 1$ using a commercial instrument (Prep LC/system 500) and commercially available columns.

INTRODUCTION

Dehydration of dihydromanool (1) and manool (2) affords a mixture of the labdadienes 3, 4 and 5 (from 1) and the labdatrienes 6, 7 and 8 (from 2) whose separation on a preparative scale by conventional chromatographic methods is cumbersome and gives only poor yields of the pure isomers (1). As relatively large amounts of 5, 6, 7 and 8 were required for biomimetic-type syntheses (2,3) the use of high performance liquid chromatography was investigated. It was found that extensive use of the peak shaving-re-

cycle technique permitted rapid separation of the labdadiene and labdatriene isomers with $\alpha \sim 1$ in high purity and high yield. As the separations provide an excellent illustration of the technique itself and its merits, we think it worth while to describe them here.



MATERIALS AND METHODS

A Waters Associates Prep LC/System 500 liquid chromatograph was used under the following conditions.

Solvent system: n-hexane

Flow rate: 0.25 ℓ/min

Chart speed: 2 min/cm

Radial compression pressure: 400 psi

Column: Two Prep PAC-500/SILICA cartridges (5.7 cm x 30 cm)

n-Hexane was distilled, filtered and degassed at reduced pressure prior to use. Samples dissolved in 5-8 ml of hexane were injected with a 10 ml gas tight syringe. Collections were evaporated under reduced pressure and monitored by NMR spectrometry at 270 MHz using a Bruker HX-270 MHz NMR spectrometer. Separation of the signals characteristic of the various isomers at 60 MHz was inadequate.

Labdadienes: 14,15-Dihydromanool (1), prepared by selective hydrogenation of manool (2) using diimide, was dehydrated by the procedure of Carman and Dennis (1). Flash chromatography of the product over silica gel gave a mixture of labdadienes 3, 4 and 5 (ca. 2:5:3 by NMR spectrometry).

Labdatrienes: Dehydration of manool (2) (1) and flash chromatography over silica gel gave a mixture of 6, 7 and 8 (ca. 5:3:11 by NMR spectrometry).

RESULTS AND DISCUSSION

Labdadienes

The mixture of 3, 4 and 5 obtained by dehydration of 1 showed a single spot on silica gel plates. Injection of 1.8 g of the mixture followed by several recycles did not indicate any separation (Fig. 1). Peak shaving in the fifth recycle afforded 3 (purity >90%) and 5 (purity > 99%), 4 being in the middle to-

gether with 3 and 5. Hence α is slightly greater than 1 although there was no apparent separation as seen by inspection of Fig. 1. Subsequent peak shaving and recycling (i.e. collect-recycle-collect) afforded pure 5 and mixtures of 3 and 4 in various proportions till recycle 11 showing that the difference between k' of 3 and 4 is very small and that $\alpha_{3,5} \geq \alpha_{4,5} > \alpha_{3,4}$.

After recycle 11 no 3 was left on the column. Further use of the peak shaving-recycle routine afforded 4 (purity > 95%) in addition to pure 5 until recycle 19. Further use of the procedure afforded only pure 5 and mixtures of 4 and 5. From the fifth cycle on, the right hand side shavings contained only 5, whereas the left hand side shavings initially contained 3, then, from cycle 6-11, mixtures of 3 and 4, then, from cycle 12-19, 4 and finally 4 and 5 showing that $V_5 > V_4 \geq V_3$. Overall, injection of 1.8 g of the mixture and 20 peak shaving-recycle repetitions afforded 0.07 g of 3 (> 90%), 0.35 g of 4 (> 95%) and 0.47 g of 5 (> 99%), with a consumption of only 12.8 ℓ of solvent in 2 hr, since after each collect-recycle-collect routine the solvent was recycled. The flow through the detector was also collected leading to recovery of 0.2 g of a mixture of 3, 4 and 5. Together with the pure compounds and mixture from collections 3, 5, 7, 9, 11, 13, 31, 33, and 34 this

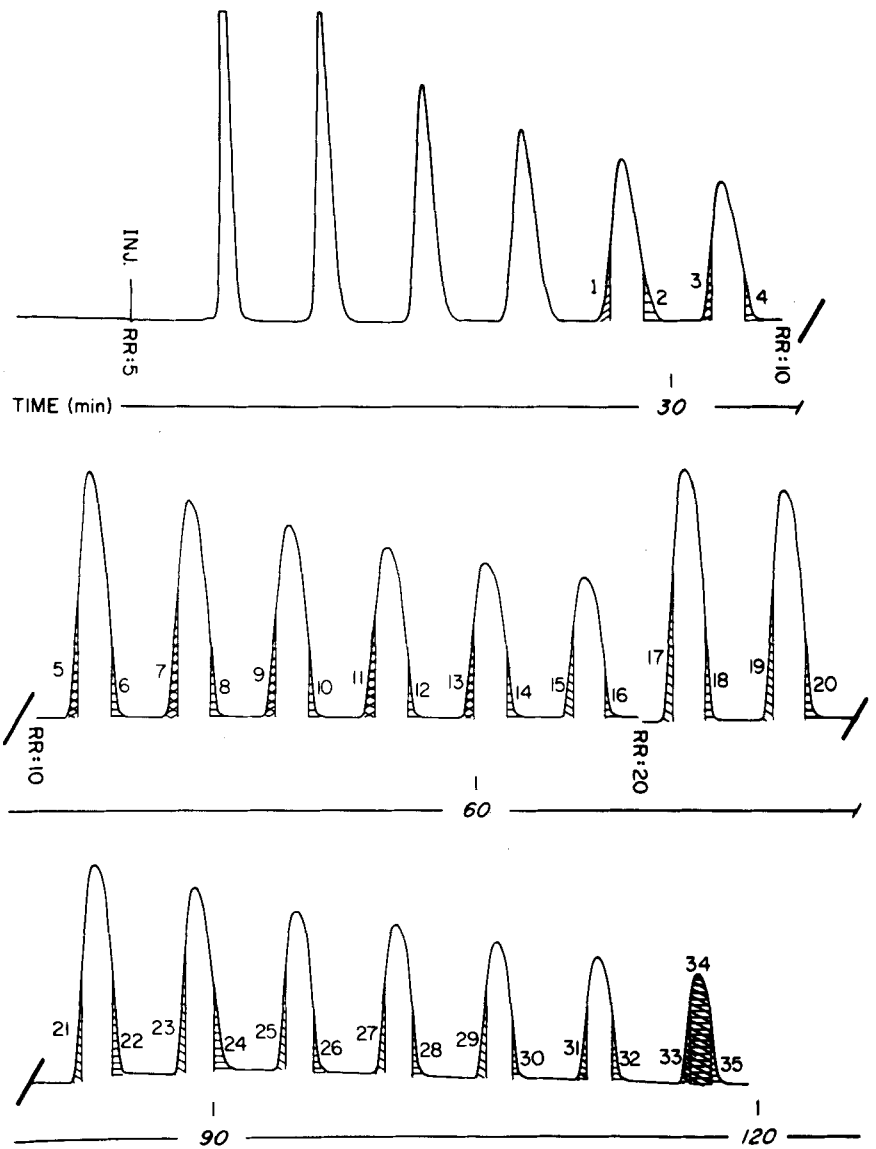


FIGURE 1. Separation of labdadienes 3, 4, and 5. Collection 1: 3. Collections 3, 5, 7, 9, 11, and 13: Mixture of 3 and 4. Collections 15, 17, 19, 21, 23, 25, 27, and 29: 4. Collections 31, 33, and 34: Mixture of 4 and 5. Collections 2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26, 28, 30, 32, and 35: 5.

constituted recovery of > 98% of starting material. Solvent recovered from the collections and waste was redistilled for further use.

Labdatrienes

The mixture of 6, 7 and 8 obtained by the dehydration of 2 showed overlapping spots on silica gel plates, but hplc separation even in the second recycle was better than for the dienes as shown in Fig. 2.

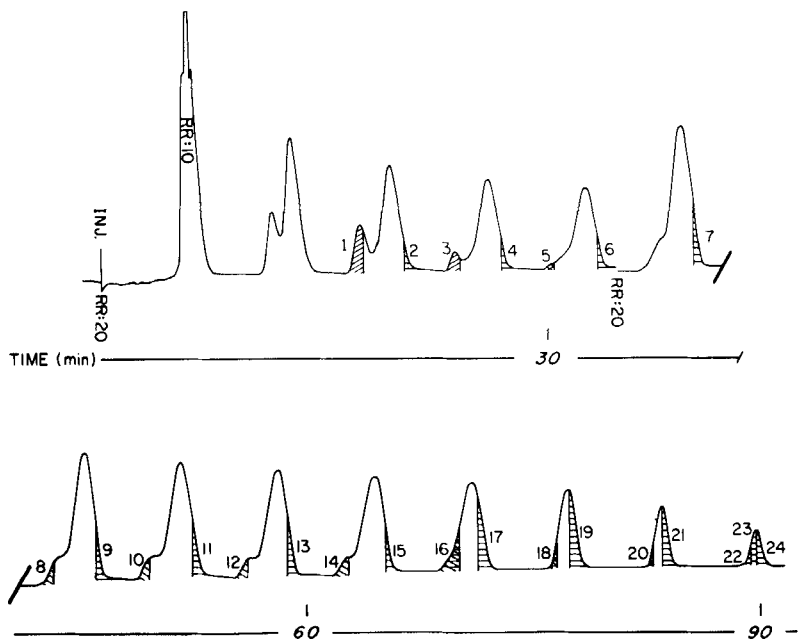


FIGURE 2. Separation of labdatrienes 6, 7, and 8. Collections 1 and 3: 6. Collection 5: Mixture of 6 and 7. Collections 8, 10, 12, and 14: 7. Collections 16, 18, and 20: Mixtures of 7 and 8. Collections 2, 4, 6, 7, 9, 11, 13, 15, 17, 19, 21, 22, 23, and 24: 8.

Peak shaving in the third and fourth recycles afforded pure 6 and 8, while the fifth recycle gave 8 and a mixture of 6 and 7. At this point all 6 was off the column. Further recycling improved the separation of 7 from 8 and peak shaving in recycles 7-10 led to isolation of pure 7 in addition to 8. Collections in recycles 11-13 gave pure 8 and mixtures of 7 and 8 in different proportions. The last peak contained only 8. The right hand side shavings always contained 8 whereas the left hand side shavings initially contained 6, then little of 6 and 7, then 7 and finally 7 and 8 showing that $V_8 > V_7 > V_6$ ($\alpha_{6,8} > \alpha_{6,7} > \alpha_{7,8}$). Flow through the detector was also collected as a mixture. Solvent was recovered and redistilled for further use.

Overall, injection of 0.75 g of the mixture followed by 13 peak shaving-recycles consumed 12.5 ℓ of solvent in 1.5 hr and permitted isolation of 0.17 g of 6, 0.07 g of 7 and 0.34 g of 8 in pure form (77%); the remaining material (23%) was recovered as a mixture. This contrasts with a 26.6% yield of isomers from column chromatography over alumina impregnated with silver nitrate (1).

CONCLUSION

The separation of the labdadiene and labdatriene isomers described in the present communication illu-

strates the great utility of the peak shaving-recycle technique for the rapid separation, on a preparative scale, of very closely related double bond isomers with $\alpha=1$.

When the technique is applied extensively, it permits the efficient separation of such compounds without modification of commercially-available apparatus or expensive adsorbents.

ACKNOWLEDGEMENT

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