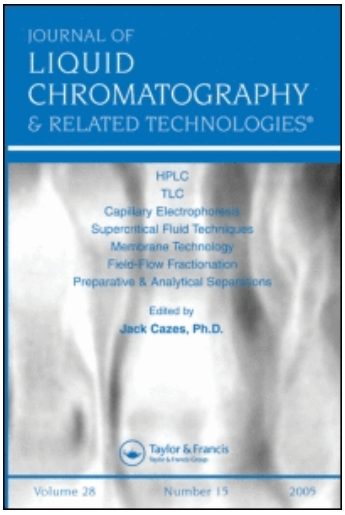

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Sechoing Lin[a]; Phillip L. Brower[a]; Derick D. Winkle[a]
[a] Chemical Development Department, Parke-Davis Pharmaceutical Research Division Warner-Lambert Company, Michigan

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CHIRAL HPLC SEPARATIONS FOR PROCESS DEVELOPMENT OF S-(+)-ISOBUTYL GABA, A POTENTIAL ANTI-EPILEPTIC AGENT

Sechoing Lin,* Phillip L. Brower, Derick D. Winkle

Chemical Development Department
Parke-Davis Pharmaceutical Research Division
Warner-Lambert Company
188 Howard Avenue
Holland, Michigan 49424

ABSTRACT

In order to develop an economically-viable route to make S-(+)-isobutyl GABA ((S)3-aminomethyl-5-methylhexanoic acid), many intermediates required chiral analyses to determine their enantiomeric purities. Multiple chiral stationary phases were employed for this purpose. Chiralcel OD-H and Chiralpak AD columns resolved more than 80 % of the tested intermediates.

INTRODUCTION

S-(+)-Isobutyl GABA, shown in Figure 1, is presently under active development as a potential anti-epileptic agent at Parke Davis. Earlier routes to produce it were extremely costly. Our goal was to find a cost-competitive route to produce the compound. Several synthetic routes were explored and reported.[1] Chiral methods were required for (a) screening of chiral agents for chemical resolution, (b) screening products from enzymatic resolutions, (c) purity determination of the resolving chiral agent, and (d) purity determination of the product. Rapid and direct chiral methodology was vitally needed.

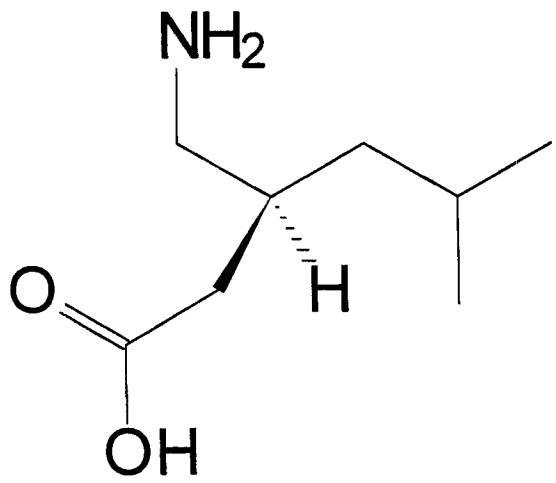


Figure 1. Structure of (S)-(+)-isobutyl GABA.

Chiral HPLC methods for process development of other potential drugs using cellulose carbamate-based and crown ether stationary phases were described previously.[2,3] In this work, we have extended the use of other polysaccharide based stationary phases for chiral separation of various intermediates encountered during the process development to produce (S)-(+)-isobutyl GABA.

EXPERIMENTAL

Apparatus

The liquid chromatographic system consisted of a Hitachi L-6200 intelligent pump, a Micromeritics 728 autosampler and a Valco injector with a 20 μL loop, a Hitachi L-4000H variable wavelength UV detector and a Waters 410 differential refractometer in series, and a Hitachi D-2500 Chromato-Integrator.

The chiral columns are Chiralcels OD, OD-H, OJ, Chiralpak AD, and Crownpak CR(+). They are all 250 x 4.6mm I.D. except the Crownpak column which is 150 x 4.0 mm I.D. They were purchased from Chiral Technologies, Inc., Exton, PA.

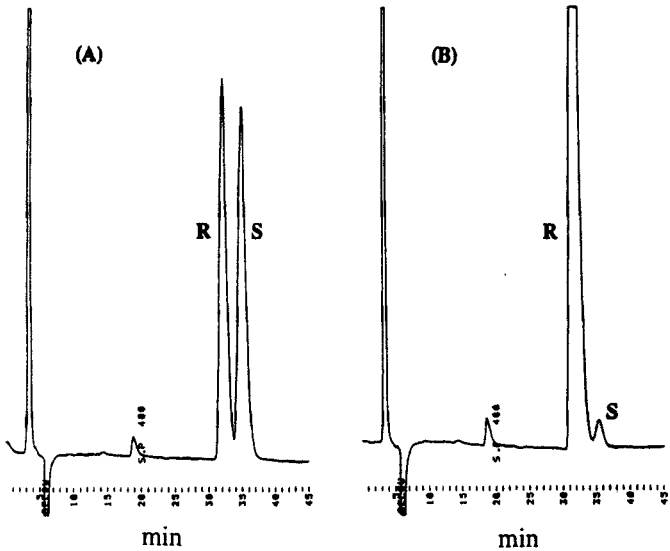


Figure 2. Separation of (A) a racemic mixture and (B) an enriched sample of 3-carbamoylmethyl-5-methylhexanoic acid, compound **13** using the conditions given in Table 1.

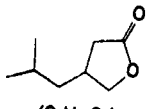
Chemicals

Hexane and isopropanol (HPLC grades) were obtained from EM Science, Gibbstown, NJ. Formic acid (88%) was purchased from J. T. Baker Inc., Phillipsburg, NJ. (S)-(+)Mandelic acid, DL-mandelic acid, (R)-(+)-1-phenylethylamine, (±)-1-phenylethylamine, (R)(+)-1-(4-chlorophenyl)-ethylamine and (S)-(-)-1-(4-chlorophenyl)-ethylamine were purchased from Zeeland Chemical, Zeeland, MI. All other compounds of interest were synthesized by the Chemical Development Department, Parke-Davis Pharmaceutical Research Division, Holland, MI.

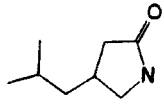
Chromatographic Conditions

The preparation of mobile phase depended upon the type of column used. For Chiralcel OD, OD-H, OJ and Chiralpak AD columns, the mobile phase was either hexane/isopropanol or hexane/isopropanol with a small amount of formic acid added. For the Crown ether column, the mobile phase was aqueous perchloric acid or aqueous perchloric acid/methanol. The detection was RI unless otherwise stated. The amount of sample injected was 50 to 100 μg. The flow rate was varied.

Compounds Studied



($C_8H_{14}O_2$)
1



($C_8H_{14}NO$)
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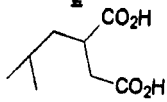
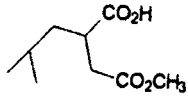
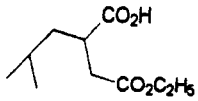


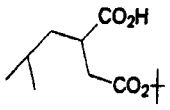
($C_8H_{14}O_4$)
3



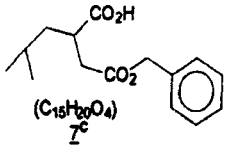
($C_9H_{16}O_4$)
4



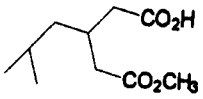
($C_{10}H_{18}O_4$)
5



($C_{12}H_{22}O_4$)
6[c]



($C_{15}H_{20}O_4$)
7[c]



($C_{10}H_{18}O_4$)
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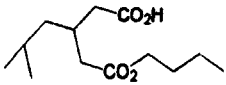

($C_{13}H_{24}O_4$)
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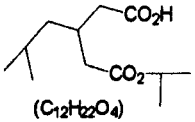

($C_{12}H_{22}O_4$)
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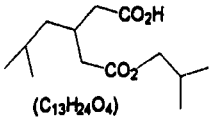

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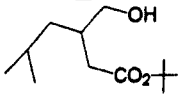

($C_{12}H_{24}O_3$)
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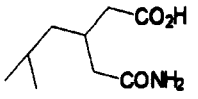
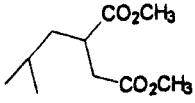


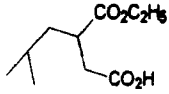
($C_9H_{17}NO_3$)
13[c]



($C_{10}H_{18}O_4$)
14

(continued)

Compounds Studied (continued)



($C_{10}H_{18}O_4$)
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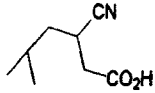

($C_8H_{13}NO_2$)
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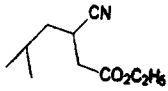

($C_{10}H_{17}NO_2$)
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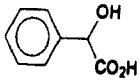
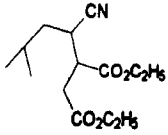


($C_8H_8O_3$)
18[c]



($C_{14}H_{23}NO_4$)
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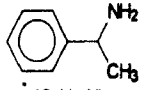
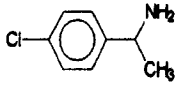
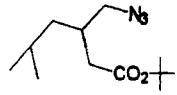


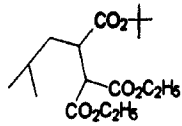
($C_8H_{11}N$)
20[c]



($C_8H_{10}ClN$)
21[c]



($C_{12}H_{23}N_3O_2$)
22



($C_{17}H_{30}O_6$)
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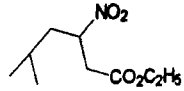
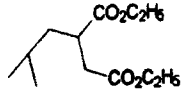
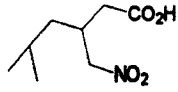


($C_9H_{17}NO_4$)
24



($C_{12}H_{22}O_4$)
25



($C_8H_{15}NO_4$)
26[c]

Table 1

Enantiomeric Separations for Various Compounds Encountered During Process Development of (S)-(+)-Isobutyl GABA[c,e]

Compound	Type of Column	Mobile Phase[a]	Flow[b]	k'_1[d]	α[d]	R_s[d]
1	Chiralpak AD	hexane/IPA (99/1)	1.0	4.30	1.13	2.10
2	Chiralpak AD	hexane/IPA (97/3)	1.0	4.11	1.17	1.64
3	Chiralcel OD-H	hexane/IPA/HCO_2H (95/5/0.1)	1.0	1.33	1.46	3.38
4	Chiralcel OD-H	hexane/IPA/HCO_2H (98.5/1.5/0.1)	1.0	3.16	1.38	4.92
5	Chiralcel OD-H	hexane/IPA/HCO_2H (99/1/0.1)	0.5	3.69	1.06	1.22
6	Chiralpak AD	hexane/IPA/HCO_2H (97/3/0.1)	1.0	1.03	2.28	5.02
7	Chiralcel OD	hexane/IPA/HCO_2H (80/20/0.1)	0.5	0.24	2.27	2.35
8	Chiralcel OD-H	hexane/IPA/HCO_2H (98.5/1.5/0.1)	1.0	4.86	1.09	1.27
9	Chiralpak AD	hexane/IPA/HCO_2H (100/1/0.1)	1.0	4.17	1.11	1.16
10	Chiralcel OJ	hexane/IPA/HCO_2H (100/1/0.1)	0.5	2.47	1.09	0.92
11	Chiralcel OD-H	hexane/IPA/HCO_2H (98/2/0.1)	0.3	1.13	1.10	1.98
12	Chiralcel OD-H	hexane/IPA/HCO_2H (100/0.5/0.1)	0.5	3.21	1.09	1.62

(continued)

Table 1 (continued)

Compound	Type of Column	Mobile Phase[a]	Flow[b]	k'_1[d]	α[d]	R_s[d]
13	Chiralcel OD-H	hexane/IPA/HCO_2H (96/4/0.1)	1.0	10.14	1.11	1.49
14	Chiralcel OD-H	hexane/IPA/HCO_2H (98.5/1.5/0.1)	1.0	0.76	2.54	7.79
15	Chiralcel OD-H	hexane/IPA/HCO_2H (95/5/0.1)	0.5	0.53	1.74	5.68
16	Chiralcel OD-H	hexane/IPA/HCO_2H (98/2/0.1)	1.0	5.39	1.07	1.17
17	Chiralcel OD-H	hexane/IPA (98/2)	0.5	1.15	1.13	1.47
18	Chiralcel OD-H	hexane/IPA/HCO_2H (95/5/0.1)	1.0	3.80	1.22	1.96
19	Chiralcel OD-H	hexane/IPA (98/2)	0.5	1.14	1.13	1.64
20	Crownpak CR(+)	aq. $HClO_4$ (pH 1.5)	1.0	7.15	1.51	2.96
21	Crownpak CR(+)	CH_3OH/aq. $HClO_4$ (10/90; pH 1.5)	1.2	13.98	1.53	3.22
22	Chiralpak AD	hexane/IPA (100/1)	0.5	0.60	1.28	1.19
23	Chiralpak AD	hexane/IPA (98/2)	0.6	0.71	1.86	7.23
24	Chiralcel OD-H	hexane/IPA/HCO_2H (100/0.5/0.1)	1.0	1.73	1.10	1.35
25	Chiralcel OD-H	hexane/IPA/HCO_2H (95/5/0.1)	0.5	0.27	2.21	5.10

(continued)

Table 1 (continued)

Compound	Type of Column	Mobile Phase[a]	Flow[b]	k'_1[d]	α[d]	R_s[d]
26	Chiralcel OD-H	hexane/IPA/HCO_2H (80/20/0.1)	1.0	1.53	1.34	2.53

[a] The ratio is volume ratio; IPA = isopropanol.
[b] Flow rate is in mL/min.
[c] Detection is UV @ 214 nm for compounds **13**, **20**, **21** and **26**; 220 nm for compound **7**; 225 nm for compound **6**; 235 nm for compound **18**.
[d] k'_1 is the capacity factor of the first eluted enantiomer; α is the stereoselectivity; R_s is the resolution factor.
[e] Structures of the compounds studied are as given above.

RESULTS AND DISCUSSION

The chiral recognition mechanism for the polysaccharide derivative based stationary phases is not clear. Their abilities to achieve the discrimination of enantiomers appears to depend on the conformation of the main chain and the structure of the substituents.[4] Numerous examples have demonstrated the applications of this type of column for chiral resolution.[5] We have found some of these columns very useful for our chiral analytical work.

Table 1 gives k'_1, α, and R_s along with the conditions for the compounds resolved. We believe these are the first direct chiral HPLC separations for these compounds reported, with the exception of mandelic acid and 1-phenylethylamine.[5]

Mobile phase consisted of hexane/isopropanol for most non-carboxylic acid containing compounds. For carboxylic acid-containing compounds, the addition of a small amount of formic acid in the mobile phase was required to facilitate elution. Optimization of the resolution was carried out by decreasing the amount of isopropanol in the mobile phase, changes in flow rate or combinations of both. As expected, greater enantiomeric resolution is achieved when one of the functional groups is adjacent to the chiral center;[6] see compounds **4** and **8**. Under the same conditions, compound **4** has greater α (1.38) and R_s (4.92) than compound **8** (α = 1.09, R_s = 1.27) although compound **4** has a shorter retention time.

3-Carbamoylmethyl-5-methylhexanoic acid, compound **13**, was incorporated into one potential process to produce (S)-(+)isobutyl GABA. We also used Chiralcel OJ and AD columns for the attempted enantiomeric determination of this compound. However, the best separation obtained using

these two columns gave only partial resolution. The enantiomeric separations of a racemic mixture and an enriched sample for this compound are given in Figures 2(A) and 2(B), respectively.

CONCLUSIONS

Direct chiral HPLC technique has become an increasingly important tool in new drug development. It has become an indispensible analytical technique for process development of a chiral drug. We have demonstrated this using a combination of chiral stationary phases for process development of S-(+)-isobutyl GABA. In particular, the use of Chiralcel OD-H and Chiralpak AD columns enabled us to resolve more than 80 % of the tested intermediates.

ACKNOWLEDGMENTS

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